

TETRAHYDROCARBAZOLE DERIVATIVES AND THEIR PHARMACEUTICAL USE

FIELD OF THE INVENTION

5 The present invention relates to novel compounds that are useful in the treatment of human papillomaviruses, and also to the methods for the making and use of such compounds.

BACKGROUND OF THE INVENTION

10 Human Papillomaviruses (HPVs) are small nonenveloped DNA viruses involved in many conditions and diseases. For example HPVs cause a wide variety of benign and pre-malignant tumors.

15 HPV is spread by direct contact. HPVs may be divided into two categories: cutaneous and mucosal. The cutaneous HPVs cause warts on hands and feet, such as common, plantar, filiform, or flat warts. The mucosal HPV types infect the anogenital region and the oral cavity. Approximately 100 different types of HPV have been characterized to date. Approximately 40 HPV types specifically infect the 20 genital and oral mucosa.

Mucosal HPVs are most frequently sexually transmitted and, with an incidence roughly twice that of herpes simplex virus infection, HPVs are considered one of the most common sexually transmitted diseases (STDs) throughout the 25 world.

Infection with the human papillomavirus (HPV) may not cause any symptoms and does not always produce visible genital warts. When symptoms do develop, they usually occur 2 to 3 months after infection with the virus. Symptoms have been known to develop, however, from 3 weeks to many years after infection occurs. As 25 such, HPV may be spread unknowingly.

More than 25 HPV types that are implicated in anogenital diseases are broadly classified as either low risk or high risk. Low risk HPVs, such as HPV-6 and HPV-11, are the etiological cause of genital warts (condyloma acuminata). High risk HPVs, such as HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, usually do 30 not produce visible genital warts. Rather the high-risk viral types may be identified by DNA testing. High risk HPVs such as HPV-16 and HPV-18 may be found on Pap screening tests and be related to precancerous cervical cell change, cervical dysplasia, and cervical cancer. In fact, high-risk HPV types, such as 16, 18, 31, 33, and 35, are strongly associated with precancerous and cancerous changes of the 35 cervix. Most cervical cancers (about 90%) contain one of these high-risk types. High

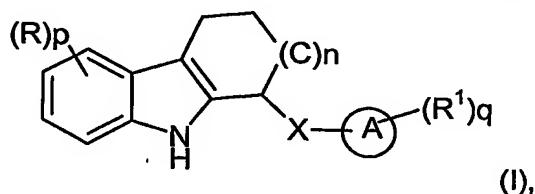
risk HPV infection creates a lifetime risk of invasive cancer in the range of 5-10% for untreated infection.

In addition to cervical cancer, high risk HPVs are associated with a number of anal and perianal cancers.

5 Current treatments for genital warts and cervical dysplasia include physical removal such as cryotherapy, electrosurgery, and surgical excision. Currently, there are no effective antiviral treatments for HPV infection.

SUMMARY OF THE INVENTION

10 The present invention includes compounds of formula (I):



wherein:

n is 0, 1, or 2;

X is NH, O, or S(O)_m;

15 each R is the same or different and is independently selected from the group consisting

of halogen, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, -R¹⁰cycloalkyl, Ay, -NHR¹⁰Ay, Het, -NHHet, -NHR¹⁰Het, -OR², -OAy, -OHet, -R¹⁰OR², -NR²R³, -NR²Ay, -R¹⁰NR²R³, -R¹⁰NR²Ay, -R¹⁰C(O)R², -C(O)R², -CO₂R², -R¹⁰CO₂R², -C(O)NR²R³, -C(O)Ay, -C(O)NR²Ay, -C(O)Het, -C(O)NHR¹⁰Het, -R¹⁰C(O)NR²R³, -C(S)NR²R³, -R¹⁰C(S)NR²R³, -R¹⁰NHC(NH)NR²R³, -C(NH)NR²R³, -R¹⁰C(NH)NR²R³, -S(O)₂NR²R³, -S(O)₂NR²Ay, -R¹⁰SO₂NHCOR², -R¹⁰SO₂NR²R³, -R¹⁰SO₂R², -S(O)_mR², cyano, nitro, or azido;

25 each R¹ is the same or different and is independently selected from the group consisting of halogen, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl,

cycloalkenyl, -R¹⁰cycloalkyl, Ay, -NHR¹⁰Ay, Het, -NHHet, -NHR¹⁰Het, -OR², -OAy, -OHet, -R¹⁰OR², -NR²R³, -NR²Ay, -R¹⁰NR²R³, -R¹⁰NR²Ay, -R¹⁰C(O)R², -C(O)R², -CO₂R², -R¹⁰CO₂R², -C(O)NR²R³, -C(O)Ay, -C(O)NR²Ay, -C(O)Het, -C(O)NHR¹⁰Het, -R¹⁰C(O)NR²R³, -C(S)NR²R³, -R¹⁰C(S)NR²R³, -R¹⁰NHC(NH)NR²R³, -C(NH)NR²R³, -R¹⁰C(NH)NR²R³, -S(O)₂NR²R³, -

$S(O)_2NR^2Ay$, $-R^{10}SO_2NHCOR^2$, $-R^{10}SO_2NR^2R^3$, $-R^{10}SO_2R^2$, $-S(O)_mR^2$, cyano, nitro, or azido;

each m independently is 0, 1, or 2;

each R^{10} is the same or different and is independently selected from alkylene,

5 cycloalkylene, alkenylene, cycloalkenylene, and alkynylene;

p and q are each independently selected from 0, 1, 2, 3, 4, or 5;

each of R^2 and R^3 are the same or different and are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, $-R^{10}cycloalkyl$, $-R^{10}OH$, $-R^{10}(OR^{10})_w$, and $-R^{10}NR^4R^5$;

10 w is 1-10;

each of R^4 and R^5 are the same or different and are independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, and alkynyl;

Ay represents an aryl group;

Het represents a 5- or 6-membered heterocycl or heteroaryl group;

15 ring A is aryl or heteroaryl;

including pharmaceutically acceptable salts, solvates, and physiologically functional derivatives thereof.

Preferably X is NH.

Preferably the reference to alkyl include C_1-C_6 alkyl, references to alkoxy

20 include C_1-C_6 alkoxy, and references to haloalkyl include C_1-C_6 haloalkyl.

In one embodiment, at least p or q is not 0. In another embodiment both p and q are each 1. In one embodiment p is 1 and q is 0 to 2.

Preferably n is 0, 1, or 2. More preferably n is 1.

Preferably R is selected from halogen, alkyl, haloalkyl, cycloalkyl, -

25 $R^{10}cycloalkyl$, Ay, Het, $-OR^2$, $-R^{10}OR^2$, $-NR^2R^3$, $-COR^2$, $-CO_2R^2$, $-CONR^2R^3$, $-$

$S(O)_2NR^2R^3$, cyano, nitro, or azido. More preferably R is selected from halogen,

alkyl, haloalkyl, cycloalkyl, $-R^{10}cycloalkyl$, Ay, Het, $-R^{10}OR^2$, $-NR^2R^3$, $-COR^2$,

$-CONR^2R^3$, $-S(O)_2NR^2R^3$, or cyano. Still more preferably R is selected from halogen,

alkyl, or haloalkyl. In one embodiment R is substituted *para* to the depicted N atom.

30 In another embodiment R is Cl or Br and is substituted *para* to the depicted N atom.

Preferably R^1 selected from halogen, alkyl, haloalkyl, Ay, Het, $-OR^2$, $-R^{10}OR^2$, $-NR^2R^3$, $-COR^2$, $-CO_2R^2$, $-CONR^2R^3$, $-S(O)_2NR^2R^3$, $-S(O)_mR^2$, cyano, nitro, or azido.

More preferably R^1 is selected from halogen, alkyl, haloalkyl, $-OR^2$, cyano, or nitro.

In one embodiment preferably q is 1 or 2, more preferably 1.

In one embodiment preferably the A ring is aryl. More preferably the A ring is phenyl.

In another embodiment preferably the A ring is heteroaryl. More preferably the heteroaryl is pyrimidinyl, pyridyl, or benzothiazolyl. More preferably the heteroaryl is pyrimidinyl or pyridyl. Further, preferably q is 0 to 2.

In one embodiment when p is not 0, then each R is the same or different and is independently selected from the group consisting of halogen, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, -R¹⁰cycloalkyl, Ay, -NHR¹⁰Ay, Het, -NHHet, -NHR¹⁰Het, -R¹⁰OR², -NR²R³, -NR²Ay, -R¹⁰NR²R³, -R¹⁰NR²Ay, -R¹⁰C(O)R², -C(O)R², -CO₂R², -R¹⁰CO₂R², -C(O)NR²R³, -C(O)Ay, -C(O)NR²Ay, -C(O)Het, -C(O)NHR¹⁰Het, -R¹⁰C(O)NR²R³, -C(S)NR²R³, -R¹⁰C(S)NR²R³, -R¹⁰NHC(NH)NR²R³, -C(NH)NR²R³, -R¹⁰C(NH)NR²R³, -S(O)₂NR²R³, -S(O)₂NR²Ay, -R¹⁰SO₂NHCOR², -R¹⁰SO₂NR²R³, -R¹⁰SO₂R², -S(O)_mR², cyano, nitro, or azido.

Particularly preferred compounds of the present invention include:

- 15 6-Bromo-N-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Chloro-N-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Chloro-N-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Chloro-N-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Chloro-N-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 20 6-Chloro-N-(4-methylphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Bromo-N-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Bromo-N-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Bromo-N-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Bromo-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride
- 25 6-Chloro-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Chloro-N-(4,6-dimethoxypyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Chloro-N-(4-methylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Chloro-N-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Bromo-N-pyridin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride
- 30 6-Bromo-N-(5-propylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Methoxy-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- 6-Methoxy-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
- N-(4,6-Dimethoxypyrimidin-2-yl)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride

6-Bromo-*N*-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride

6-Bromo-*N*-[5-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-*N*-[5-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

5 6-[(6-Bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl)amino]nicotinonitrile

N-(1,3-Benzothiazol-2-yl)-6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

N-Pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

2-Bromo-*N*-pyrimidin-2-yl-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-amine

6-Methyl-*N*-pyridin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride salt

10 Methyl 1-anilino-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate

6-[(6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl)amino]nicotinonitrile hydrochloride salt

N-Phenyl-6-(trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride

N-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

15 6-Bromo-*N*-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-*N*-(3-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-*N*-(1*H*-indol-5-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-*N*-(2-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-*N*-(2-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

20 6-Bromo-*N*-(2-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-*N*-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine; and

6-Bromo-*N*-(4-fluorophenoxy)-2,3,4,9-tetrahydro-1*H*-carbazole.

More particularly preferred compounds include:

25 6-Bromo-*N*-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Chloro-*N*-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Chloro-*N*-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Chloro-*N*-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Chloro-*N*-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Chloro-*N*-(4-methylphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

30 6-Bromo-*N*-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-*N*-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-*N*-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-*N*-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride

6-Chloro-*N*-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

35 6-Chloro-*N*-(4,6-dimethoxypyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

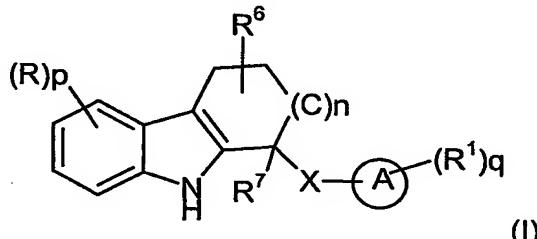
6-Chloro-*N*-(4-methylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Chloro-*N*-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-pyridin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride
6-Bromo-*N*-(5-propylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
5 *N*-(4,6-Dimethoxypyrimidin-2-yl)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride
6-Bromo-*N*-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride
6-Bromo-*N*-[5-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
10 6-Bromo-*N*-[5-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-[(6-Bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl)amino]nicotinonitrile
N-(1,3-Benzothiazol-2-yl)-6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
2-Bromo-*N*-pyrimidin-2-yl-5,6,7,8,9,10-hexahydrocyclohepta[b]indol-6-amine
6-Methyl-*N*-pyridin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride salt
15 Methyl 1-anilino-2,3,4,9-tetrahydro-1*H*-carbazole-6-carboxylate
6-[(6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl)amino]nicotinonitrile hydrochloride salt
N-Phenyl-6-(trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride
N-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
20 6-Bromo-*N*-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(3-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(2-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(2-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(2-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
25 6-Bromo-*N*-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine; and
6-Bromo-*N*-(4-fluorophenoxy)-2,3,4,9-tetrahydro-1*H*-carbazole.

More particularly preferred compounds include:

6-Bromo-*N*-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Chloro-*N*-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
30 6-Chloro-*N*-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Chloro-*N*-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Chloro-*N*-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Chloro-*N*-(4-methylphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
35 6-Bromo-*N*-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-N-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
N-Phenyl-6-(trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride
N-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
5 6-Bromo-*N*-(3-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(2-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(2-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(2-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
6-Bromo-*N*-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine; and
10 6-Bromo-*N*-(4-fluorophenoxy)-2,3,4,9-tetrahydro-1*H*-carbazole.

Another embodiment of the present invention includes:



including salts, solvates and pharmaceutically functional derivatives wherein

R^6 is H, alkyl, $-OR^2$, $-NR^2R^3$, Ay, Het, $-C(O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-S(O)_mR^2$, or oxo,

15 where R^2 and R^3 are as defined above; and

R^7 is H or alkyl; provided R^6 and R^7 are not both H.

Another aspect of the present invention includes pharmaceutical compositions comprising one or more compounds of the present invention and a pharmaceutically acceptable carrier.

20 Another aspect of the present invention includes a compound of the present invention for use as an active therapeutic substance.

Another aspect of the present invention includes a compound of the present invention for use in the treatment or prophylaxis of diseases and conditions caused by oncogenic viruses, including adenoviruses, retroviruses, and papovavirus family, 25 including polyoma viruses and papilloma viruses.

Another aspect of the present invention includes a compound of the present invention for use in the treatment or prophylaxis of conditions or disorders due to HPV infection. Particularly, the condition or disease is warts, genital warts, cervical dysplasia, recurrent respiratory papillomatosis, or cancers associated with 30 papillomavirus infection. More particularly the cancer is anogenital cancers, head and neck cancers, and skin cancers. More particularly the anogenital cancers are

cervical, anal and perianal, vulvar, vaginal, and penile cancers; the head and neck cancers are oral pharyngeal region and esophagus cancers; and the skin cancers are basal cell carcinoma and squamous cell carcinoma.

Another aspect of the present invention includes the use of a compound of the present invention in the manufacture of a medicament for use in the treatment or prophylaxis of oncogenic viruses, including adenoviruses, retroviruses, and papovavirus family, including polyoma viruses and papilloma viruses. Thus, the present invention includes the use of a compound of the present invention in the manufacture of a medicament for use in the treatment or prophylaxis of conditions or disorders due to HPV infection. More particularly the condition or disorder is warts, genital warts, cervical dysplasia, recurrent respiratory papillomatosis, or cancers associated with papillomavirus infection.

Another aspect of the present invention includes a method for the treatment or prophylaxis of oncogenic viruses, adenoviruses, retroviruses, small DNA tumor viruses of the adenovirus and papovavirus family (such as polyoma viruses and papilloma viruses) comprising the administration of a compound of the present invention. Thus, the present invention includes a method for the treatment or prophylaxis of conditions or disorders due to HPV infection comprising the administration of a compound of the present invention. More particularly, the condition or disorder is warts, genital warts, cervical dysplasia, recurrent respiratory papillomatosis, or cancers associated with papillomavirus infection.

As noted herein, p and q are each independently defined as 0, 1, 2, 3, 4, or 5. Notably, as will be appreciated by those skilled in the art, the value(s) of p and/or q should not exceed the substitutable positions on the depicted rings.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Terms are used within their accepted meanings. The following definitions are meant to clarify, but not limit, the terms defined.

As used herein the term "alkyl" refers to a straight or branched chain

5 hydrocarbon, preferably having from one to twelve carbon atoms, that may be optionally substituted, with multiple degrees of substitution included within the present invention. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, tert-butyl, isopentyl, n-pentyl, and substituted versions thereof.

10 As used throughout this specification, the preferred number of atoms, such as carbon atoms, will be represented by, for example, the phrase " C_xC_y alkyl," which refers to an alkyl group, as herein defined, containing the specified number of carbon atoms. Similar terminology will apply for other preferred terms and ranges as well.

15 As used herein the term "alkenyl" refers to a straight or branched chain aliphatic hydrocarbon containing one or more carbon-to-carbon double bonds that may be optionally substituted, with multiple degrees of substitution included within the present invention. Examples include, but are not limited to, vinyl, allyl, and the like and substituted versions thereof.

20 As used herein the term "alkynyl" refers to a straight or branched chain aliphatic hydrocarbon containing one or more carbon-to-carbon triple bonds that may be optionally substituted, with multiple degrees of substitution included within the present invention. Examples include, but are not limited to, ethynyl and the like and substituted versions thereof.

25 As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical, preferably having from one to ten carbon atoms. Alkylene groups as defined herein may optionally be substituted, with multiple degrees of substitution included within the present invention. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene, and substituted versions thereof.

30 As used herein, the term "alkenylene" refers to a straight or branched chain divalent hydrocarbon radical, preferably having from one to ten carbon atoms, containing one or more carbon-to-carbon double bonds that may be optionally substituted, with multiple degrees of substitution included within the present invention. Examples include, but are not limited to, vinylene, allylene or 2-propenylene, and the like and substituted versions thereof.

As used herein, the term "alkynylene" refers to a straight or branched chain divalent hydrocarbon radical, preferably having from one to ten carbon atoms, containing one or more carbon-to-carbon triple bonds that may be optionally substituted, with multiple degrees of substitution included within the present invention. Examples include, but are not limited to, ethynylene and the like and substituted versions thereof.

As used herein, the term "cycloalkyl" refers to an optionally substituted non-aromatic cyclic hydrocarbon ring, which optionally includes an alkylene linker through which the cycloalkyl may be attached, with multiple degrees of substitution included within the present invention. Exemplary "cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and substituted versions thereof. As used herein, the term "cycloalkyl" includes an optionally substituted fused polycyclic hydrocarbon saturated ring and aromatic ring system, namely polycyclic hydrocarbons with less than maximum number of non-cumulative double bonds, for example where a saturated hydrocarbon ring (such as a cyclopentyl ring) is fused with an aromatic ring (herein "aryl," such as a benzene ring) to form, for example, groups such as indane.

As used herein, the term "cycloalkenyl" refers to an optionally substituted non-aromatic cyclic hydrocarbon ring containing one or more carbon-to-carbon double bonds which optionally includes an alkylene linker through which the cycloalkenyl may be attached, with multiple degrees of substitution included within the present invention. Exemplary "cycloalkenyl" groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and substituted versions thereof.

As used herein, the term "cycloalkylene" refers to a divalent, optionally substituted non-aromatic cyclic hydrocarbon ring, with multiple degrees of substitution included within the present invention. Exemplary "cycloalkylene" groups include, but are not limited to, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, and substituted versions thereof.

As used herein, the term "cycloalkenylene" refers to a divalent optionally substituted non-aromatic cyclic hydrocarbon ring containing one or more carbon-to-carbon double bonds, with multiple degrees of substitution included within the present invention. Exemplary "cycloalkenylene" groups include, but are not limited to, cyclopropenylene, cyclobutenylene, cyclopentenylene, cyclohexenylene, cycloheptenylene, and substituted versions thereof.

As used herein, the term "heterocycle" or "heterocyclyl" refers to an optionally substituted mono- or polycyclic ring system containing one or more degrees of unsaturation and also containing one or more heteroatoms. Preferred heteroatoms include N, O, and/or S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to twelve-membered and is either fully saturated or has one or more degrees of unsaturation. Multiple degrees of substitution are included within the present definition. Such rings may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" groups include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, 5 pyrrolidine, morpholine, tetrahydrothiopyran, and tetrahydrothiophene.

As used herein, the term "aryl" refers to an optionally substituted benzene ring or to an optionally substituted fused benzene ring system, for example anthracene, phenanthrene, or naphthalene ring systems. Multiple degrees of substitution are included within the present definition. Examples of "aryl" groups include, but are not 10 limited to, phenyl, 2-naphthyl, 1-naphthyl, and substituted derivatives thereof.

As used herein, the term "heteroaryl" refers to an optionally substituted monocyclic five to seven membered aromatic ring, or to an optionally substituted fused bicyclic aromatic ring system comprising two of such aromatic rings. These heteroaryl rings contain one or more nitrogen, sulfur, and/or oxygen atoms, where N-oxides, sulfur oxides, and dioxides are permissible heteroatom substitutions. Multiple 20 degrees of substitution are included within the present definition. Examples of "heteroaryl" groups used herein include, but should not be limited to, furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, 25 pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, indazole, benzimidizolyl, imidazopyridinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, and substituted versions thereof.

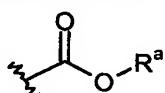
As used herein the term "halogen" refers to fluorine, chlorine, bromine, or iodine.

As used herein the term "haloalkyl" refers to an alkyl group, as defined herein, that is substituted with at least one halogen. Examples of branched or straight 30 chained "haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, and t-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo, and iodo. The term "haloalkyl"

should be interpreted to include such substituents as perfluoroalkyl groups and the like.

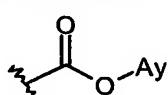
As used herein the term "alkoxy" refers to the group $-OR^a$, where R^a is alkyl as defined above.

5 As used herein the term "alkoxycarbonyl" refers to groups such as:



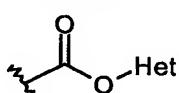
where the R^a represents an alkyl group as herein defined.

As used herein the term "aryloxycarbonyl" refers to groups such as:



10 where the Ay represents an aryl group as herein defined.

As used herein the term "heteroaryloxycarbonyl" refers to groups such as:



where the Het represents a heteroaryl group as herein defined.

As used herein the term "nitro" refers to the group $-NO_2$.

15 As used herein the term "cyano" refers to the group $-CN$.

As used herein the term "azido" refers to the group $-N_3$.

As used herein the term "acyl" refers to the group $R^bC(O)-$, where R^b is alkyl, aryl, heteroaryl, or heterocyclyl, as each is defined herein.

As used herein the term "oxo" refers to the group $=O$.

20 Also, as used herein throughout the present specification, the phrase "optionally substituted" or variations thereof denote an optional substitution, including multiple degrees of substitution, with one or more substituent group. The phrase should not be interpreted as duplicative of the substitutions herein described and depicted. Exemplary optional substituent groups include acyl; alkyl; alkenyl; alkynyl; alkylsulfonyl; alkoxy; alkoxycarbonyl; cyano; halogen; haloalkyl; hydroxy; nitro; aryl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; heteroaryl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; arylsulfonyl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; heteroarylsulfonyl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; heteroarylsulfonyl, which may be further substituted with acyl,

alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; aryloxy, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; heteroaryloxy, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; aryloxycarbonyl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; heteroaryloxycarbonyl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; or $-\text{N}(\text{R}')_2$; where for each occurrence R' is independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkylsulfonyl, arylsulfonyl, or heteroarylsulfonyl, where each occurrence of such aryl or heteroaryl may be substituted with one or more acyl, alkoxy, alkyl, alkenyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro, or the two R' 's may combine to form a ring, optionally having additional heteroatoms, optionally having one or more degrees of unsaturation, and optionally being further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro.

The compounds of formulas (I) may crystallize in more than one form, a characteristic known as polymorphism, and such polymorphic forms ("polymorphs") are within the scope of formula (I). Polymorphism generally can occur as a response to changes in temperature, pressure, or both. Polymorphism can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

Certain of the compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I), as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

Typically, but not absolutely, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term

"pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts. Representative salts include acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, calcium edetate, camsylate, carbonate, 5 clavulanate, citrate, dihydrochloride, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, 10 pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclinate, tosylate, triethiodide, trimethylammonium, and valerate salts. Other salts, which are not pharmaceutically acceptable, may be useful 15 in the preparation of compounds of this invention and these should be considered to form a further aspect of the invention.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula I, or a salt or physiologically functional derivative thereof) and a solvent. Such solvents, for the purpose of the invention, should not interfere with the biological activity of the solute.

20 Non-limiting examples of suitable solvents include, but are not limited to water, methanol, ethanol, and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Non-limiting examples of suitable pharmaceutically acceptable solvents include water, ethanol, and acetic acid. Most preferably the solvent used is water.

25 As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention that, upon administration to a mammal, is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives, for example, esters and amides, will be clear to those skilled in the art, without undue 30 experimentation. Reference may be made to the teaching of *Burger's Medicinal Chemistry And Drug Discovery*, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

35 As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue,

system, animal, or human that is being sought, for instance, by a researcher or clinician. The term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. For use in therapy, therapeutically effective amounts of a compound of formula (I), as well as salts, solvates, and physiological functional derivatives thereof, may be administered as the raw chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition.

Accordingly, the invention further provides pharmaceutical compositions that include effective amounts of compounds of the formula (I) and salts, solvates, and physiological functional derivatives thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof, are as herein described. The carrier(s), diluent(s) or excipient(s) must be acceptable, in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient of the pharmaceutical composition.

In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula (I) or salts, solvates, and physiological functional derivatives thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors. For example, the species, age, and weight of the recipient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration are all factors to be considered. The therapeutically effective amount ultimately should be at the discretion of the attendant physician or veterinarian. Regardless, an effective amount of a compound of formula (I) for the treatment of humans suffering from frailty, generally, should be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day. More usually the effective amount should be in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70 kg adult mammal the actual amount per day would usually be from 70 to 700 mg. This amount may be given in a single dose per day or in a number (such as two, three, four, five, or more) of sub-doses per day such that the total daily dose

is the same. An effective amount of a salt, solvate, or physiologically functional derivative thereof, may be determined as a proportion of the effective amount of the compound of formula (I) *per se*. Similar dosages should be appropriate for treatment of the other conditions referred to herein.

5 Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, as a non-limiting example, 0.5mg to 1g of a compound of the formula (I), depending on the condition being treated, the route of administration, and the age, weight, and condition of the patient. Preferred unit dosage formulations are those containing a
10 daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

15 Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by an oral (including buccal or sublingual), rectal,
15 nasal, topical (including buccal, sublingual or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). By way of example, and not meant to limit the invention, with regard to
20 certain conditions and disorders for which the compounds of the present invention are believed useful certain routes will be preferable to others. Based upon the physical manifestations that are often associated with HPV infection, rectal, topical, or vaginal routes of administration may be preferable. As one example, for the treatment or prophylaxis of cervical dysplasia the preferred route may be a vaginal route.
25

30 Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions, each with aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions. For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Generally, powders are prepared by comminuting the compound to a suitable fine size and mixing with an appropriate pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or

mannitol. Flavorings, preservatives, dispersing agents, and coloring agents can also be present.

Capsules are made by preparing a powder, liquid, or suspension mixture and encapsulating with gelatin or some other appropriate shell material. Glidants and

5 lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the mixture before the encapsulation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested. Moreover, when desired or necessary, suitable binders,

10 lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Examples of suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants useful in these dosage forms include, for

15 example, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets.

20 A powder mixture may be prepared by mixing the compound, suitably comminuted, with a diluent or base as described above. Optional ingredients include binders such as carboxymethylcellulose, alginates, gelatins, or polyvinyl pyrrolidone, solution retardants such as paraffin, resorption accelerators such as a quaternary salt, and/or absorption agents such as bentonite, kaolin, or dicalcium phosphate. The powder

25 mixture can be wet-granulated with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials, and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet-forming dies by means of

30 the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric

material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solutions, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound.

5 Syrups can be prepared, for example, by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated generally by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives; flavor

10 additives such as peppermint oil, or natural sweeteners, saccharin, or other artificial sweeteners; and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, 15 wax or the like.

The compounds of formula (I) and salts, solvates, and physiological functional derivatives thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, 20 such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled.

The compounds may also be coupled with soluble polymers as targetable 25 drug carriers. Such polymers can include polyvinylpyrrolidone (PVP), pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethyl-aspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug; for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, 30 polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be 35 presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active

ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6), 318 (1986), incorporated herein by reference as related to such delivery systems.

5 Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

10 For treatments of the eye or other external tissues, for example mouth and skin, the formulations may be applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

15 Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

20 Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouthwashes.

25 Pharmaceutical formulations adapted for nasal administration, where the carrier is a solid, include a coarse powder having a particle size for example in the range 20 to 500 microns. The powder is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

30 Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered dose pressurized aerosols, nebulizers, or insufflators.

35 Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

40 Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

45 Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which

may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question. For example, formulations suitable for oral administration 10 may include flavoring or coloring agents.

The compounds of the present invention and their salts, solvates, and physiologically functional derivatives thereof, may be employed alone or in combination with other therapeutic agents. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately 15 and, when administered separately, administration may occur simultaneously or sequentially, in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. The administration in combination of a compound of formula (I) salts, solvates, or 20 physiologically functional derivatives thereof with other treatment agents may be in combination by administration concomitantly in: (1) a unitary pharmaceutical composition including both compounds; or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is 25 administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

The compounds of the present invention may be used in the treatment of a variety of disorders and conditions and, as such, the compounds of the present invention may be used in combination with a variety of other suitable therapeutic 30 agents useful in the treatment or prophylaxis of those disorders or conditions. Treatment will depend upon the nature and type of HPV infection. As discussed briefly above, treatment for warts can be divided into ablative and medical approaches. The compounds of the present invention may be combined with either or both approaches.

Ablative methods include classic surgical excision and destruction by electrodesiccation, laser, or liquid nitrogen. Thus, the compounds of the present invention may be used in conjunction with such methods or upon reoccurrence after such methods.

5 Alternatively, the present invention may be combined with other medical therapies including a variety of cytotoxic or antiviral agents. For example, and not meant to limit the invention, the compounds of the present invention may be combined with other therapeutic agents such as 5-fluorouracil, retinoic acid, podophyllin, podofilox, keratolytic agents such as salicylic acid and/or lactic acid, 10 haptens such as diphenacyprone (DPC), squaric acid dibutyl ester (SADBE) or dinitrochlorobenzene (DNCB), formalin, topical trichloroacetic acid, topical tretinoin, cidofovir, imiquimod and/or cytokines such as interferon alfa-2b.

15 One aspect of the present invention is the use of the compounds of the present invention for the treatment or prophylaxis of a variety of disorders including, but not limited to, diseases and conditions caused by oncogenic viruses (such as adenoviruses, papovaviruses, retroviruses), and in particular the small DNA tumor viruses of the adenovirus and papovavirus family (polyoma and papilloma) and more particularly papilloma viral infections. The present invention includes administering to a subject in need thereof a therapeutically effective amount of a compound of formula 20 (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

25 More specifically, the present invention includes the treatment or prophylaxis of conditions or diseases associated with papilloma viral infections. These conditions and diseases include warts (e.g. plantar warts), genital warts, recurrent respiratory papillomatosis (laryngeal papillomas), and cancers associated with papillomavirus infection. Cancers that have been associated with papillomavirus infection include 30 anogenital cancers (cervical, anal and perianal, vulvar, vaginal, penile cancers), head and neck cancers (oral pharyngeal region, esophagus), and skin cancers (basal cell carcinoma, squamous cell carcinoma). The present invention includes administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a salt, solvate or physiologically functional derivative thereof.

35 The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

In all of the examples described below, protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of synthetic chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) *Protecting Groups in Organic Synthesis*, John Wiley & Sons, incorporated by reference with regard to protecting groups). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I).

Those skilled in the art will recognize if a stereocenter exists in compounds of formula (I). Accordingly, the present invention includes all possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a compound is desired as a single enantiomer, such may be obtained by stereospecific synthesis, by resolution of the final product or any convenient intermediate, or by chiral chromatographic methods as are known in the art. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, *Stereochemistry of Organic Compounds* by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994), incorporated by reference with regard to stereochemistry.

EXPERIMENTAL SECTION

Abbreviations:

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
μ L (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
Hz (Hertz);	MHz (megahertz);
mol (moles);	mmol (millimoles);
RT (room temperature);	h (hours);
min (minutes);	TLC (thin layer chromatography);
mp (melting point);	RP (reverse phase);

Tr (retention time);	TFA (trifluoroacetic acid);
TEA (triethylamine);	THF (tetrahydrofuran);
TFAA (trifluoroacetic anhydride);	CD ₃ OD (deuterated methanol);
CDCl ₃ (deuterated chloroform);	DMSO (dimethylsulfoxide);
5 SiO ₂ (silica);	atm (atmosphere);
EtOAc (ethyl acetate);	CHCl ₃ (chloroform);
HCl (hydrochloric acid);	Ac (acetyl);
DMF (N,N-dimethylformamide);	Me (methyl);
Cs ₂ CO ₃ (cesium carbonate);	EtOH (ethanol);
10 Et (ethyl);	tBu (tert-butyl);
MeOH (methanol).	

Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted at room temperature unless otherwise noted.

15 ¹H NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, or a General Electric QE-300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

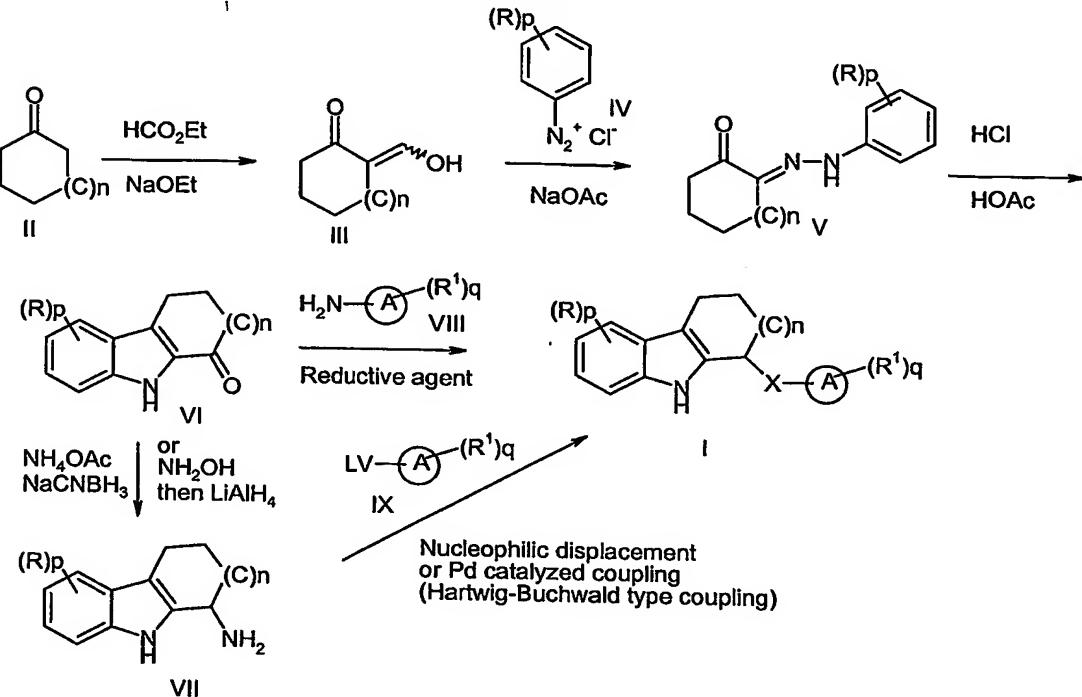
20 Mass spectra were obtained on Micromass Platform or ZMD mass spectrometers from Micromass Ltd., Altricham, UK, using wither Atmospheric Chemical Ionization (APCI) or Electrospray Ionization (ESI).

Analytical thin layer chromatography was used to verify the purity of intermediate(s) which could not be isolated or which were too unstable for full characterization as well as to follow the progress of reaction(s).

Compounds of formula (I), wherein common terms are as defined above and LV is a leaving group such as halogen (F, Cl, Br, I), SO₂Ar, SO₂Ar^a, where R^a is an alkyl group, may be conveniently prepared by the process outlined in Scheme 1 below:

5

Scheme 1



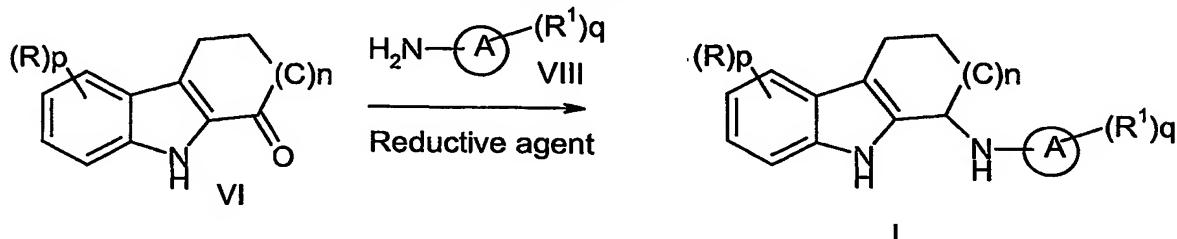
Generally, the process for preparing the compounds of formula (I), where LV is a leaving group as defined above and X is NH (all formulas and all other variables having been defined above) comprises the steps of:

10 a) reacting a compound of formula (II) with ethyl formate;
 b) reacting the compound of formula (III) with diazocompound of formula (IV);
 c) indolizing the compound of formula (V) to prepare a compound of formula (VI);
 d) reductive amination of compound of formula (VI) to form compound of formula (VII); and
 15 e) forming compounds of formula (I) from compound (VII) by nucleophilic displacement or by using palladium catalyzed coupling conditions.

Alternatively

f) forming compounds of formula (I) via reductive amination of compound (VI).

More specifically, a compound of formula (I), wherein all variables are as defined above, can be prepared reacting the compound of formula (VI) with an amine of formula (VIII) in the presence of a reducing agent:



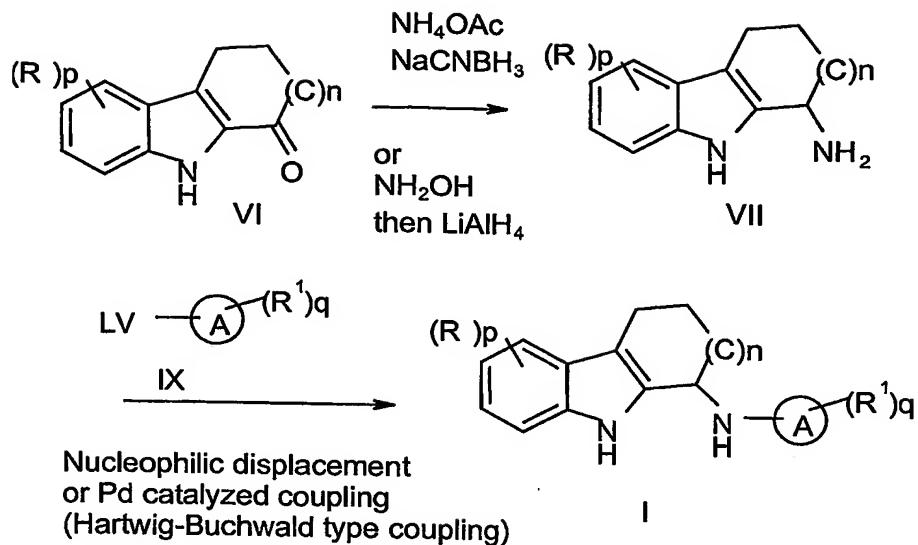
5 again, where all variables are as herein defined.

The reaction may be carried out as a two step process where the imine is formed under conditions that allow for removal of water followed by reduction. Alternatively this reaction can be carried out in one pot by adding amine (VIII) and the reductive agent sequentially or at the same time.

10 For the two step process, typically a compound of formula (VI) is dissolved in an inert solvent such as toluene, an equivalent, or an excess of an amine of formula (VIII) is added, followed by the optional addition of an acid catalyst such as para-toluenesulfonic acid. The reaction is heated to reflux for azeotropic removal of water. Optionally molecular sieves or dehydrating agents, such as trimethylorthoformate, 15 can be used for removal of water.

The imine can be isolated or used directly for the next step. The imine is dissolved in a suitable solvent and reduced by addition of a reductive agent. Suitable solvents include lower alcohols such as methanol, ethanol, and the like, tetrahydrofuran, or similar solvents well known to those skilled in the art. Suitable 20 reductive agents include but are not limited to sodium cyanoborohydride, sodium triacetoxyborohydride, borane-tetrahydrofuran complex, sodium borohydride, and the like.

For a one pot process, a compound of formula (VI) is dissolved in an inert solvent. An amine of formula (VIII) is added to this solution, followed by the addition 25 of a suitable reductive agent. The reaction may optionally be heated to about 50-150°C. Suitable solvents include but are not limited to, dichloromethane, dichloroethane, and the like. Suitable reductive agents include but are not limited to sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, and the like.



Alternatively a compound of formula (I) can be formed from an amine of formula (VII). Treatment of compound of formula (VI) in an inert solvent with ammonium salt and a reductive agent, optionally with heating, gives an amine of formula (VII). Suitable solvents include but are not limited to, methanol, ethanol, dichloromethane, dichloroethane, and the like. Suitable reductive agents include but are not limited to sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, and the like. Suitable ammonium salts include but are not limited to ammonium acetate, ammonium formate, and the like. An amine of formula (VII) can also be formed by treatment of compound of formula (VI) with hydroxylamine, followed by reduction with suitable reductive agents which include but are not limited to lithium aluminium hydride and the like.

Condensation of compound of formula (VII) with compound of formula (IX) gives compound of formula (I). This condensation can be carried out neat or in the presence of solvent, optionally with heating or in a microwave. Suitable solvents include but are not limited to N,N-dimethylformamide, 1-methyl-2-pyrrolidinone, dimethylsulfoxide, acetonitrile, nitromethane and the like. Optionally a base can be added to the condensation reaction, examples of suitable bases include sodium carbonate, sodium bicarbonate, triethylamine, and the like.

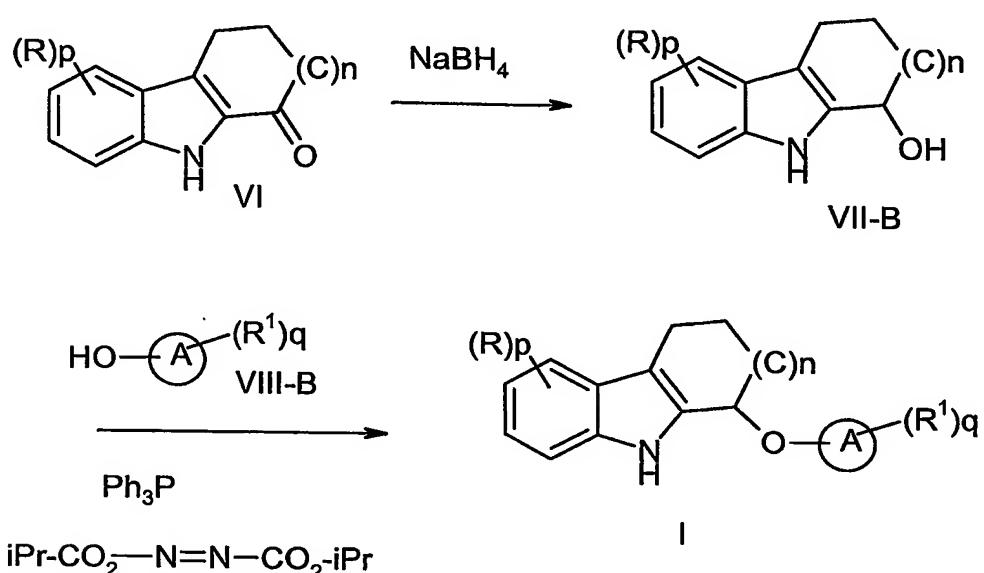
In addition, as depicted above, an amine of formula (VII) may be coupled with a compound of formula (IX) to give a compound of formula (I), using appropriate Pd-catalyzed coupling as is appreciated in the art.

Compounds of formula (VI) are prepared in a similar fashion as described in the literature (J. Med. Chem. 1973, 16, 425 and J. Org. Chem. 1968, 32, 1265).

As will be appreciated by those skilled in the art, a compound of formula (I) can be converted to another compound of formula (I).

5

Scheme II



Generally the process for preparing compound of formula (I) where X is O consists of :

1. Reduction of compound of formula (VI) to give compound of formula VII-B

10 2. Reaction of compound of formula VII-B with compound of formula VIII-B to give compound of formula I (where all variable substituents are as herein defined).

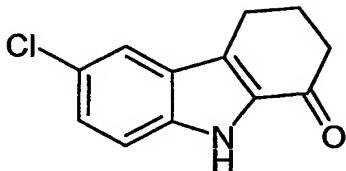
More specifically compound of formula (VII-B) wherein all variables are defined as above can be prepared by reduction of compound of formula (VI). A suitable reducing agent include but are not limited to sodium borohydride, borane-

15 tetrahydrofuran complex, and the like. Suitable solvents include methanol, ethanol, tetrahydrofuran, and the like. Compound of formula (I) can be formed by reaction of compound of formula (VII-B) with a compound of formula (VIII-B) in presence of diethyl azodicarboxylate or diisopropyl azodicarboxylate and triphenylphosphine. Suitable solvents include tetrahydrofuran and the like.

20

EXAMPLES

Example 1: 6-Chloro-2,3,4,9-tetrahydro-1H-carbazol-1-one.

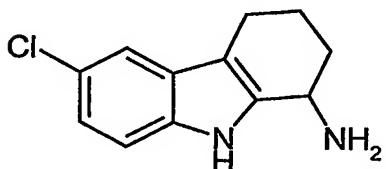


a) Cyclohexane-1,2-dione (4-chlorophenyl)hydrazone. To a cold (0°C) solution of 4-chloroaniline (5.6 g, 44 mmol) in concentrated hydrochloric acid (5 mL) was added sodium nitrite (3.0 g, 44 mmol) dissolved in water (10 mL) portionwise over 20

5 minutes. The mixture was stirred at 0°C for 30 minutes. In a separate flask, a cool solution of 2-(hydroxymethylene)cyclohexanone (Organic Syntheses, Collective Vol 4, 1963, pg. 536) (5.0 g, 40 mmol) in methanol (30 mL) was treated with a solution of sodium acetate (8.3 g, 101 mmol) in water (25 mL). The mixture was stirred at 0°C for 20 minutes and the diazonium salt slurry was added. The combined mixture was 10 stirred for 10—15 minutes, collected by filtration, triturated with ethanol, and collected by filtration to give cyclohexane-1,2-dione (4-chlorophenyl)hydrazone (4.6 g, 49% yield) as a yellow solid. ¹H-NMR (DMSO-*d*₆): δ 9.93 (s, 1H), 7.29 (m, 4H), 2.55 (m, 2H), 2.40 (m, 2H), 1.84-1.75 (m, 4H).

15 b) 6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one. A solution of cyclohexane-1,2-dione (4-chlorophenyl)hydrazone (2.3 g, 9.7 mmol) in hydrochloric acid (2 mL) and acetic acid (8 mL) was heated at 120°C for 20 minutes. The mixture was cooled slightly and treated with ice water. The resulting precipitate was collected by filtration to give 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (1.9 g, 88% yield) as brown 20 solid. ¹H-NMR (DMSO-*d*₆): δ 11.78 (s, 1H), 7.75 (m, 1H), 7.38 (d, 1H), 7.28 (dd, 1H), 2.92 (t, 2H), 2.55 (t, 2H), 2.13 (q, 2H); MS *m/z* 220 (M+1).

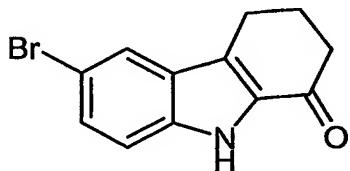
Example 2: 6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine.



25 To a solution of 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (500 mg, 2.3 mmol) and ammonium acetate (1.8 g, 23 mmol) in methanol (9 mL) was added sodium cyanoborohydride (720 mg, 11.5 mmol). After heating at 60°C for 15 hours, the mixture was cooled and treated with concentrated hydrochloric acid until pH = 1. The

organics were removed under reduced pressure and the resulting precipitate was collected by filtration, dissolved in ethyl acetate and methanol, and washed with saturated aqueous sodium carbonate. The phases were separated and the organic phase was concentrated to yield 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine 5 (260 mg, 52% yield) as a light brown solid. $^1\text{H-NMR}$ (DMSO- d_6): δ 10.90 (s, 1H), 7.34 (m, 1H), 7.27 (d, 1H), 6.97 (dd, 1H), 3.90 (t, 1H), 2.54 (m, 2H), 2.04-1.89 (m, 2H), 1.66 (m, 1H), 1.50 (m, 1H); MS m/z 221 (M+1).

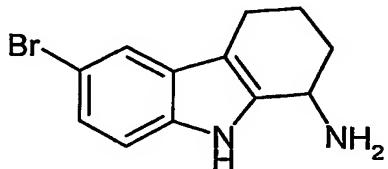
Example 3: 6-Bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one



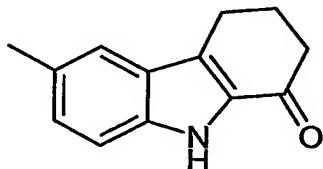
10

6-Bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one was prepared from bromoaniline and 2-(hydroxymethylene)cyclohexanone in a similar manner as described in Example 1 to give a brown solid. $^1\text{H-NMR}$ (CDCl_3): δ 8.79 (s, 1H), 7.80 (s, 1H), 7.44 (d, 1H), 7.30, (d, 2H), 2.97 (t, 2H), 2.66 (t, 2H), 2.27 (quint, 2H); MS m/z 265 (M+1).

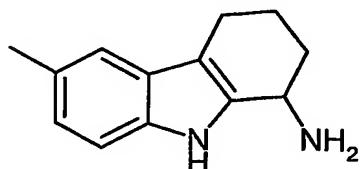
15

Example 4: 6-Bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

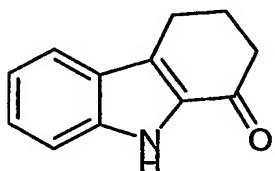
6-Bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared in a similar manner as described in Example 2 to give a solid. ¹H-NMR (CDCl₃): δ 8.58 (s, 1H), 7.55 (s, 1H), 7.20 (m, 2H), 4.12 (t, 1H), 2.70 (t, 2H), 2.24 (m, 1H), 2.05 (m, 1H), 1.92 (m, 3H), 1.66 (m, 1H); MS *m/z* 266 (M+1).

Example 5: 6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one

6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one was prepared from *p*-toluidine and 2-(hydroxymethylene)cyclohexanone in a similar manner as described in Example 1 to give a tan solid. ¹H-NMR (CDCl₃): δ 8.65 (s, 1H), 7.43 (s, 1H), 7.30 (d, 1H), 7.20 (d, 1H), 2.98 (t, 2H), 2.65 (t, 2H), 2.45 (s, 3H), 2.26 (quint, 2H); MS *m/z* 220 (M+1).

Example 6: 6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared in a similar manner as described in Example 2 to give a solid. ¹H-NMR (DMSO-d₆): δ 10.5 (s, 1H), 7.15 (d, 1H), 7.11 (s, 1H), 6.81 (d, 1H), 3.98 (t, 1H), 3.30 (s, 2H), 2.53 (t, 2H), 2.32 (s, 3H), 2.02 (m, 1H), 1.90 (m, 1H), 1.68 (m, 1H), 1.65 (m, 1H); MS *m/z* 201 (M+1).

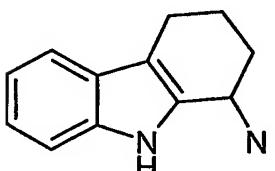
Example 7a: 2,3,4,9-Tetrahydro-1*H*-carbazol-1-one

2,3,4,9-Tetrahydro-1*H*-carbazol-1-one was prepared from aniline (2.9 g, 31 mmol) and 2-(hydroxymethylene)cyclohexanone (3.5 g, 28 mmol) in a similar manner as

5 described in Example 1 to give 2.5 g (49%) of a brown solid. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 11.6 (s, 1H), 7.66 (d, 1H), 7.38 (d, 1H), 7.30 (t, 1H), 7.07 (t, 1H), 2.90 (t, 2H), 2.56 (t, 2H), 2.15 (quint, 2H); MS *m/z* 186 (M+1).

Example 7b: 2,3,4,9-Tetrahydro-1*H*-carbazol-1-amine hydrochloride

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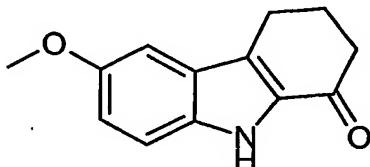


To a solution of 2,3,4,9-tetrahydro-1*H*-carbazol-1-one (1.5 g, 8.10 mmol) in ethanol (20 mL) was added a solution of hydroxylamine hydrochloride (1.13 g, 16.2 mmol) in water (10 mL) and a solution of sodium acetate (2.19 g, 26.7 mmol) in water (10 mL).

15 The reaction mixture was heated at reflux for 2 h, cooled and concentrated. The residue was diluted with water and extracted with ethyl acetate (2 x 100 mL). The organic phase was dried over sodium sulfate, filtered and concentrated to a brown solid. The oxime was dissolved in THF (80 mL) and LAH (1.0 M in THF, 24.3 mL) was added dropwise. The reaction was heated at reflux for 7 h and cooled in an ice bath. Methanol was added dropwise until bubbling ceased. The mixture was diluted with aqueous Na/K tartrate, stirred vigorously for 15 min and extracted with ethyl acetate (2 x 100 mL). The extracts were combined, dried over sodium sulfate, filtered and concentrated. The crude amine was purified by flash chromatography on silica (2% to 5% methanol/methylene chloride gradient) to provide 2,3,4,9-tetrahydro-1*H*-carbazol-1-amine as a brown oil. The oil was diluted in diethyl ether and HCl (1.0 M in diethyl ether) was added. The resulting precipitate was collected by filtration to provide 2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride (760 mg, 42%) as a light brown solid. $^1\text{H-NMR}$ (CD_3OD): δ 7.54 (d, 1H), 7.42 (d, 1H), 7.22 (t, 1H), 7.09 (t,

1H), 4.66 (t, 1H), 2.95-2.73 (m, 2H), 2.39-2.28 (m, 1H), 2.18-2.03 (m, 3H); MS *m/z* (M + 1) 170.

Example 8: 6-Methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-1-one

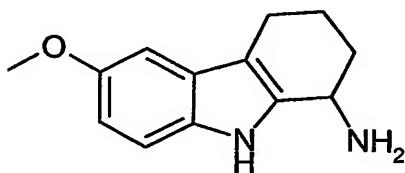


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6-Methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-1-one was prepared from *p*-anisidine and 2-(hydroxymethylene)cyclohexanone in a similar manner as described in Example 1 to give a tan solid. ¹H-NMR (CDCl₃): δ 8.77 (br s, 1H), 7.32 (d, 1H), 7.06 (d, 1H), 7.03 (s, 1H), 3.88 (s, 3H), 2.98 (t, 2H), 2.66 (t, 2H), 2.28 (quint, 2H); MS *m/z* 216 (M+1).

10

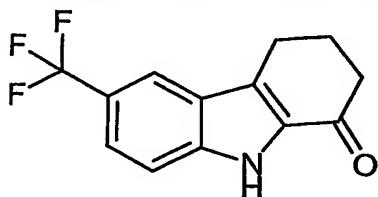
Example 9: 6-Methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine



6-Methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared in a similar manner as described above to give a solid. ¹H-NMR (CDCl₃): δ 8.38 (s, 1H), 7.20 (d, 1H), 6.92 (s, 1H), 6.80 (d, 1H), 4.06 (t, 1H), 3.85 (s, 3H), 2.67 (t, 2H), 2.18 (m, 1H), 2.00 (m, 1H), 1.83 (m, 1H), 1.60 (m, 1H); MS *m/z* 217 (M+1).

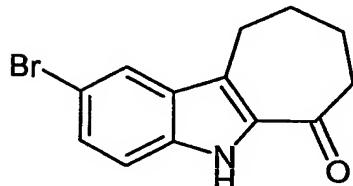
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Example 10: 6-(Trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one.



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6-(Trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one was prepared from 4-(trifluoromethyl)aniline (5.5 g, 34 mmol) and 2-(hydroxymethylene)cyclohexanone (3.9 g, 31 mmol) in a similar manner as described above to give 2.25 g (29%) of a dark brown solid. ¹H-NMR (DMSO-*d*₆): δ 12.05 (s, 1H), 8.11 (s, 1H), 7.56 (s, 2H), 3.00 (t, 2H), 2.58 (t, 2H), 2.19-2.13 (m, 2H).

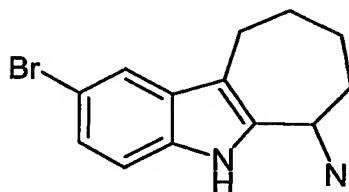
Example 11: 2-Bromo-7,8,9,10-tetrahydrocyclohepta[b]indol-6(5H)-one

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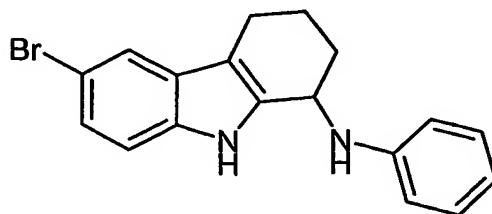
2-Bromo-7,8,9,10-tetrahydrocyclohepta[b]indol-6(5H)-one was prepared from 4-bromoaniline (7.8 g, 46 mmol) and 2-(hydroxymethylene)cycloheptanone (5.8 g, 41 mmol) in a similar manner as described in Example 1 to give 3.5 g (31%) of a dark brown solid. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$): δ 8.95 (s, 1H), 7.79 (s, 1H), 7.41 (d, 1H), 7.25 (d, 1H), 3.09 (t, 2H), 2.85 (t, 2H), 2.12-2.06 (m, 2H), 2.02-1.96 (m, 2H); MS m/z (M+1) 278, 280.

Example 12: 2-Bromo-5,6,7,8,9,10-hexahydrocyclohepta[b]indol-6-amine hydrochloride

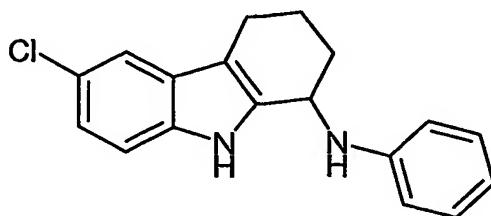
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2-Bromo-5,6,7,8,9,10-hexahydrocyclohepta[b]indol-6-amine hydrochloride was prepared from 2-Bromo-7,8,9,10-tetrahydrocyclohepta[b]indol-6(5H)-one (1.5 g, 5.4 mmol) in a similar manner as described above to give 0.98 g (57%) of a light brown solid. $^1\text{H-NMR}$ (CD_3OD): δ 7.65 (s, 1H), 7.28-7.21 (m, 2H), 4.67 (t, 1H), 3.07-3.02 (m, 1H), 2.84-2.76 (m, 1H), 2.31-2.25 (m, 1H), 2.14-1.93 (m, 4H), 1.65-1.55 (m, 1H).

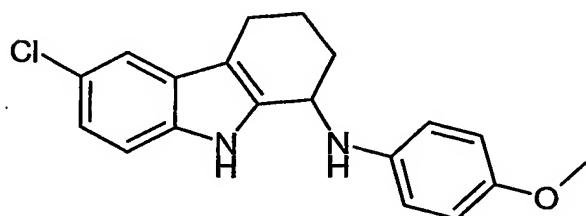
Example 13: 6-Bromo-N-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

A solution of 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (500 mg, 1.9 mmol), aniline (350 mg, 3.8 mmol) and *p*-toluenesulfonic acid (catalytic) in toluene (15 mL) was heated at reflux for 16 h with a Dean-Stark trap in place. The reaction was cooled, concentrated, and the imine was purified by flash column chromatography on silica (gradient of 5% to 50% ethyl acetate/hexanes). The imine was dissolved in methanol (10 mL) and sodium borohydride (140 mg, 3.8 mmol) was added portionwise. The reaction was stirred for 30 min and quenched with water, concentrated, and diluted with ethyl acetate. The organic phase was separated, absorbed onto diatomaceous earth and purified by flash column chromatography on silica (gradient of 2% to 20% ethyl acetate/hexanes) to provide 6-bromo-N-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine as a brown oil. ¹H-NMR (DMSO-*d*₆): δ 8.04 (s, 1H), 7.61 (s, 1H), 7.25-7.21 (m, 4H), 6.80-6.72 (m, 3H), 4.84-4.78 (m, 1H), 3.86-3.82 (m, 1H), 2.27-2.21 (m, 2H), 2.08-2.00 (m, 1H), 1.89-1.78 (m, 3H). The oil was dissolved in diethyl ether and HCl (1.0 M in diethyl ether) was added. The resulting precipitate was collected by filtration to provide 6-bromo-N-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride (352 mg, 51%) as a yellow solid. ¹H-NMR (DMSO-*d*₆): δ 11.12 (s, 1H), 7.58 (s, 1H), 7.26 (d, 1H), 7.15-7.13 (m, 3H), 6.88-6.78 (m, 2H), 6.72-6.64 (m, 1H), 4.82-4.79 (m, 1H), 2.69-2.45 (m, 2H), 1.96-1.90 (m, 2H), 1.83-1.73 (m, 2H); MS *m/z* (M-1) 339, 341.

Example 14: 6-Chloro-N-phenyl-2,3,4,9-tetrahydro-1H-carbazol-1-amine

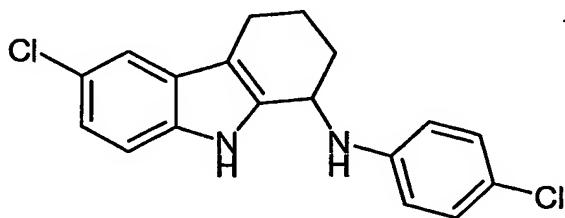
6-Chloro-N-phenyl-2,3,4,9-tetrahydro-1H-carbazol-1-amine was prepared from 6-chloro-2,3,4,9-tetrahydro-1H-carbazol-1-one and aniline in a similar manner as

5 described in Example 13 to give 200 mg (74% yield) of a yellow solid. ¹H-NMR (CDCl₃): δ 8.04 (s, 1H), 7.46 (d, 1H), 7.27-7.20 (m, 2H), 7.17 (dd, 1H), 7.10 (dd, 1H), 6.79 (m, 1H), 6.74 (m, 2H), 4.81 (m, 1H), 3.85 (s, 1H), 2.70 (m, 2H), 2.25 (m, 1H), 2.03 (m, 1H), 1.93-1.78 (m, 2H); MS m/z 295 (M-1).

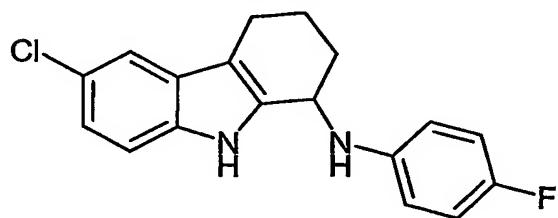
10 Example 15: 6-Chloro-N-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine

6-Chloro-N-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine was prepared from 6-chloro-2,3,4,9-tetrahydro-1H-carbazol-1-one and 4-methoxyaniline in a similar

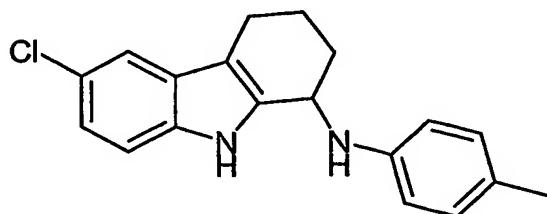
15 manner as described in Example 13 to give 32 mg (21% yield) of a brown solid. ¹H-NMR (CDCl₃): δ 8.13 (s, 1H), 7.50 (d, 1H), 7.23 (dd, 1H), 7.14 (dd, 1H), 6.92-6.84 (m, 2H), 6.79-6.73 (m, 2H), 4.76 (m, 1H), 3.83 (s, 3H), 2.74 (m, 2H), 2.28 (m, 1H), 2.08 (m, 1H), 1.98-1.75 (m, 2H); MS m/z 325 (M-1).

Example 16: 6-Chloro-N-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Chloro-N-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one and 4-chloroaniline in a similar manner as described in Example 13 to give 25 mg (16% yield) of a tan solid. ¹H-NMR (CDCl₃): δ 8.01 (m, 1H), 7.46 (d, 1H), 7.21-7.14 (m, 3H), 7.11 (dd, 1H), 6.65 (d, 2H), 4.76 (m, 1H), 2.70 (m, 2H), 2.22 (m, 1H), 2.01 (m, 1H), 1.94-1.75 (m, 2H); MS m/z 329 (M-1).

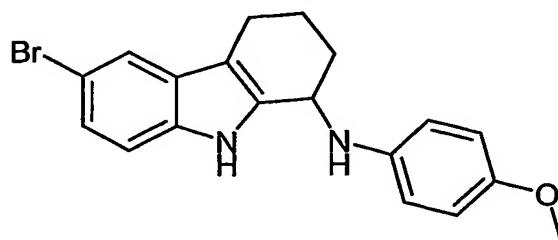
10 Example 17: 6-Chloro-N-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Chloro-N-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one and 4-fluoroaniline in a similar manner as described in Example 13 to give 63 mg (43% yield) of a yellow solid. ¹H-NMR (CDCl₃): δ 8.03 (s, 1H), 7.46 (m, 1H), 7.23-7.05 (m, 2H), 6.95 (m, 2H), 6.66 (m, 2H), 4.72 (s, 1H), 3.70 (s, 1H), 2.70 (m, 2H), 2.21 (m, 1H), 2.01 (m, 1H), 1.93-1.71 (m, 2H); MS m/z 313 (M-1).

Example 18: 6-Chloro-N-(4-methylphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

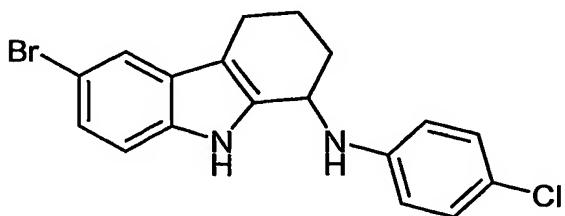
6-Chloro-N-(4-methylphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one and *p*-toluidine in a similar

5 manner as described in Example 13 to give 59 mg (41% yield) of a yellow solid. ¹H-NMR (CDCl₃): δ 8.10 (s, 1H), 7.51 (m, 1H), 7.22 (d, 1H), 7.17-7.06 (m, 3H), 6.72 (d, 2H), 4.82 (m, 1H), 3.74 (s, 1H), 2.74 (m, 2H), 2.33 (s, 3H), 2.27 (m, 1H), 2.07 (m, 1H), 1.98-1.76 (m, 2H); MS *m/z* 309 (M-1).

10 Example 19: 6-Bromo-N-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

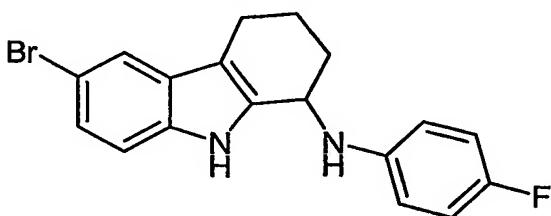
6-Bromo-N-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (100 mg, 0.38 mmol) and *p*-anisidine (94 mg, 0.76 mmol) in a similar manner as described in Example 13 to give

15 41 mg (29%) of a light brown solid. ¹H-NMR (DMSO-d₆): δ 11.05 (s, 1H), 7.54 (s, 1H), 7.22 (d, 1H), 7.11 (d, 1H), 6.73-6.66 (m, 4H), 5.48 (d, 1H), 4.70-4.65 (m, 1H), 3.63 (s, 3H), 2.66-2.53 (m, 2H), 1.98-1.89 (m, 2H), 1.79-1.71 (m, 2H); MS *m/z* (M-1) 369, 371.

Example 20: 6-Bromo-N-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-N-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (100 mg, 0.38 mmol) and 4-

5 chloroaniline (97 mg, 0.76 mmol) in a similar manner as described in Example 13 to give 29 mg (20%) of an off-white solid. $^1\text{H-NMR}$ (DMSO- d_6): δ 11.07 (s, 1H), 7.56 (s, 1H), 7.23 (d, 1H), 7.13-7.08 (m, 3H), 6.71 (d, 2H), 6.20 (d, 1H), 4.76-4.72 (m, 1H), 2.68-2.54 (m, 2H), 1.99-1.85 (m, 2H), 1.80-1.74 (m, 2H); MS m/z (M-1) 373, 375.

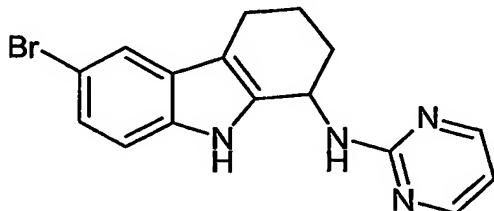
10 Example 21: 6-Bromo-N-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-N-(4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (100 mg, 0.38 mmol) and 4-

15 fluoroaniline (84 mg, 0.76 mmol) in a similar manner as described in Example 13 to give 26 mg (19%) of an off-white solid. $^1\text{H-NMR}$ (DMSO- d_6): δ 11.07 (s, 1H), 7.55 (d, 1H), 7.23 (d, 1H), 7.12 (dd, 1H), 6.92 (t, 2H), 6.70-6.68 (m, 2H), 5.89 (d, 1H), 4.73-

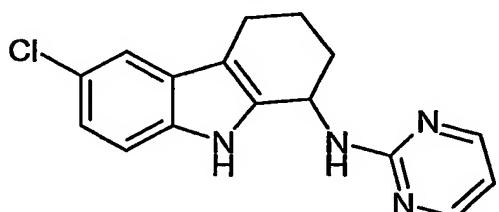
4.71 (m, 1H), 2.68-2.53 (m, 2H), 1.99-1.73 (m, 4H); MS m/z (M-1) 357, 359.

Example 22: 6-Bromo-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1H-carbazol-1-amine hydrochloride



A solution of 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (43 mg, 0.16 mmol) and 2-chloropyrimidine (56 mg, 0.49 mmol) in *N,N*-dimethylformamide (1.0 mL) was sealed in a microwave vial and heated by a Smith Synthesizer microwave at 150 °C for 15 minutes. The mixture was diluted with ethyl acetate (10 mL) and washed with water (2 x 10 mL). The organic phase was concentrated and purified by flash column chromatography on silica (20% to 50% gradient of ethyl acetate/hexanes) to provide 6-bromo-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine. The amine was diluted with diethyl ether (3 mL) and hydrogen chloride (1.0 M in diethyl ether) was added. The suspension was concentrated, diluted with acetonitrile and water, frozen and lyophilized to provide 6-bromo-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride (16 mg, 26%) as a yellow solid. ¹H-NMR (DMSO-*d*₆): δ 10.94 (s, 1H), 8.44-8.39 (m, 2H), 8.03-7.96 (m, 1H), 7.55 (s, 1H), 7.23 (d, 1H), 7.12 (d, 1H), 6.72 (t, 1H), 5.37-5.32 (m, 1H), 2.63-2.59 (m, 2H), 2.09-1.95 (m, 2H), 1.87-1.75 (m, 2H); MS *m/z* (M-1) 341, 343.

Example 23: 6-Chloro-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine



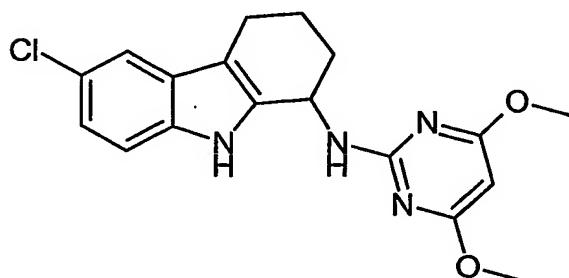
A solution of 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (50 mg, 0.23 mmol) and 2-methylsulfonylpyrimidine (69 mg, 0.44 mmol) in *N,N*-dimethylformamide (0.50 mL) was heated at 150°C for 900 seconds in a Smith Synthesizer microwave. The mixture was diluted with ethyl acetate and extracted with 5% aqueous lithium chloride. The organic layer was isolated and concentrated onto silica. Purification by

flash chromatography (0-30% ethyl acetate-hexanes) yielded 6-chloro-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (8 mg, 12% yield) as a yellow solid.

Alternatively, 6-chloro-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine could be prepared in a 9% yield by heating a mixture of 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine and 2-chlorosulfonylpyrimidine in *N,N*-dimethylformamide at 60°C for 15 hours.

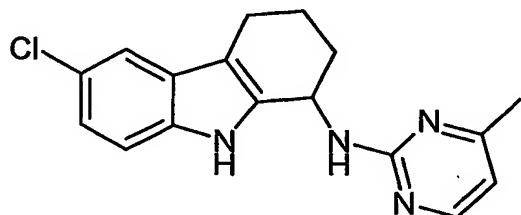
¹H-NMR (CDCl₃): δ 8.88 (s, 1H), 8.37 (m, 2H), 7.46 (m, 1H), 7.19 (d, 1H), 7.09 (dd, 1H), 6.66 (t, 1H), 5.72 (s, 1H), 5.22 (m, 1H), 2.72 (m, 2H), 2.29 (m, 1H), 2.06-1.90 (m, 3H); MS *m/z* 297 (M-1).

Example 24: 6-Chloro-N-(4,6-dimethoxypyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine



15 6-Chloro-N-(4,6-dimethoxypyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine and 4,6-dimethoxy-2-methylsulfonylpyrimidine in a similar manner as described above to give 8 mg (10% yield) of a pale yellow solid. ¹H-NMR (CDCl₃): δ 8.79 (s, 1H), 7.45 (s, 1H), 7.18 (dd, 1H), 7.08 (dd, 1H), 5.50 (s, 1H), 5.24 (m, 1H), 5.18 (m, 1H), 3.88 (2s, 6H), 2.70 (m, 2H), 2.28 (m, 1H), 2.04-1.83 (m, 3H); MS *m/z* 359 (M+1).

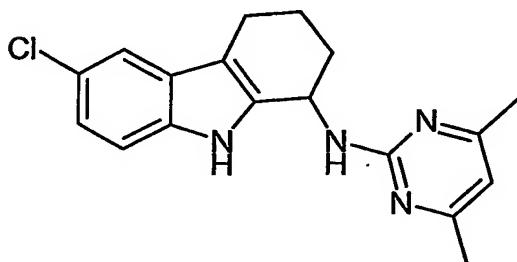
Example 25: 6-Chloro-N-(4-methylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine



6-Chloro-N-(4-methylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine and 4-methyl-2-methylsulfonylpyrimidine in a similar manner as described above to give 6 mg (7% yield) of a yellow solid. $^1\text{H-NMR}$ (CDCl_3): δ 9.05 (s, 1H), 8.23 (d, 1H), 7.45 (m, 1H), 7.17 (d, 1H), 7.07 (dd, 1H), 6.52 (d, 1H), 5.36 (m, 1H), 5.20 (m, 1H), 2.70 (m, 2H), 2.38 (s, 3H), 2.29 (m, 1H), 2.02-1.85 (m, 3H); MS m/z 311 (M-1).

10

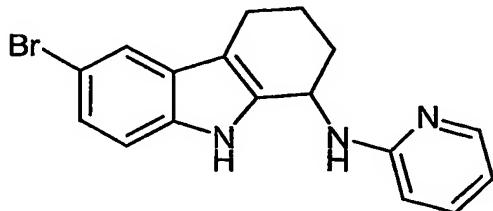
Example 26: 6-Chloro-N-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine



6-Chloro-N-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine and 2-chloro-4,6-dimethylpyrimidine in a similar manner as described above to give 6 mg (8% yield) of a pale yellow oil. $^1\text{H-NMR}$ (CDCl_3): δ 9.23 (s, 1H), 7.45 (s, 1H), 7.16 (d, 1H), 7.07 (d, 1H), 6.42 (s, 1H), 5.25 (m, 1H), 5.20 (m, 1H), 2.70 (m, 2H), 2.35 (s, 6H), 2.29 (m, 1H), 2.03-1.83 (m, 3H); MS m/z 327 (M+1).

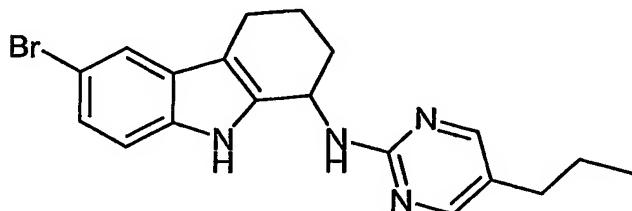
20

Example 27: 6-Bromo-N-pyridin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride

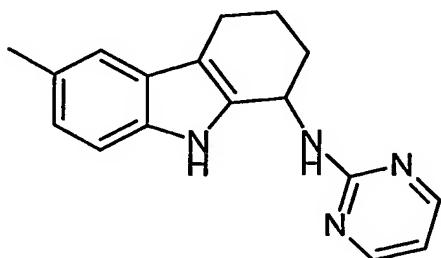


6-Bromo-N-pyridin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride was
 5 prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (150 mg, 0.57 mmol)
 and 2-aminopyridine (107 mg, 1.1 mmol) in a similar manner as described above to
 give 10 mg of a white powder as the hydrochloride salt. ¹H-NMR (DMSO-*d*₆): δ 11.20
 (s, 1H), 7.99 (d, 1H), 7.92-7.86 (m, 1H), 7.65 (s, 1H), 7.30 (d, 1H), 7.20 (d, 1H), 7.09-
 7.02 (m, 1H), 6.91-6.86 (m, 1H), 5.30-5.25 (m, 1H), 2.76-2.60 (m, 1H), 2.16-2.09 (m,
 10 1H), 1.95-1.82 (m, 3H); MS *m/z* (M-1) 340, 342.

Example 28: 6-Bromo-N-(5-propylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

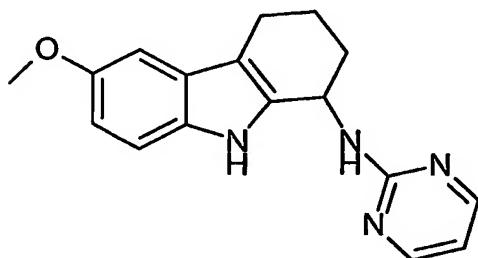


15 6-Bromo-N-(5-propylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine
 was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (75 mg, 0.28
 mmol) and 5-propyl-2-chloropyrimidine (0.5 mL) in a similar manner as described
 above to give 5 mg (5%) of a yellow solid. ¹H-NMR (DMSO-*d*₆): δ 10.86 (s, 1H), 8.17
 (s, 2H), 7.53 (s, 1H), 7.30 (d, 1H), 7.22 (d, 1H), 7.10 (d, 1H), 5.30-5.23 (m, 1H), 2.63-
 2.56 (m, 2H), 2.36 (t, 2H), 2.06-1.96 (m, 2H), 1.84-1.73 (m, 2H), 1.56-1.47 (m, 2H),
 20 0.88 (t, 3H); MS *m/z* (M-1) 383, 385.

Example 29: 6-Methyl-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1H-carbazol-1-amine

6-Methyl-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1H-carbazol-1-amine was prepared from 6-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-amine and 2-chloropyrimidine in a

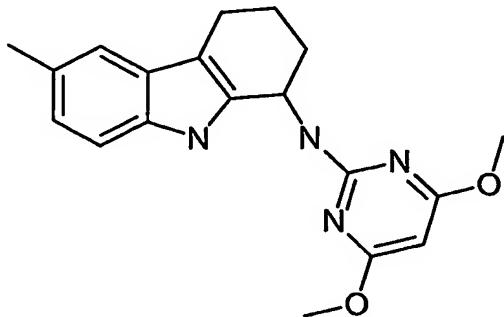
5 similar manner as described above to give 5 mg (4%) of a yellow solid. $^1\text{H-NMR}$ (CDCl_3): δ 8.63 (s, 1H), 8.40 (d, 1H), 7.32 (d, 2H), 7.24 (d, 1H), 7.01 (d, 1H), 6.64 (t, 1H), 5.47 (d, 1H), 5.24 (q, 1H), 2.74 (m, 2H), 2.44 (s, 3H), 2.36 (t, 1H), 2.00 (m, 3H); MS m/z 279 (M+1).

10 Example 30: 6-Methoxy-N-pyrimidin-2-yl-2,3,4,9-tetrahydro-1H-carbazol-1-amine

6-Methoxy-N-(5-propylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine was prepared from 6-methoxy-2,3,4,9-tetrahydro-1H-carbazol-1-amine and 2-

chloropyrimidine in a similar manner as described above to give 4 mg (4%) of a 15 yellow solid. $^1\text{H-NMR}$ (CDCl_3): δ 8.72 (s, 1H), 8.40 (d, 2H), 7.25 (d, 1H), 7.00 (s, 1H), 6.84 (d, 1H), 6.64 (t, 1H), 5.47 (d, 1H), 5.24 (q, 1H), 3.85 (s, 3H), 2.74 (m, 2H), 2.36 (t, 1H), 2.00 (m, 3H); MS m/z 295 (M+1).

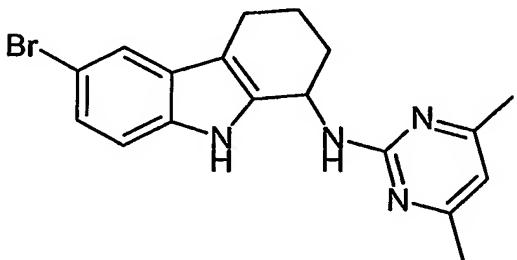
Example 31: *N*-(4,6-Dimethoxypyrimidin-2-yl)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride



N-(4,6-Dimethoxypyrimidin-2-yl)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride was prepared from 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine and 2-chloro-4,6-dimethoxypyrimidine in a similar manner as described in Example 22 to give 12 mg (8%) of a reddish solid. $^1\text{H-NMR}$ (CDCl_3): δ 10.4 (s, 1H), 7.40 (s, 1H), 7.13 (m, 2H), 6.82 (s, 1H), 5.46 (d, 1H), 5.30 (s, 1H), 4.08 (s, 6H), 2.65 (m, 2H), 2.33 (s, 3H), 2.06 (m, 2H), 1.80 (m, 2H); $\text{MS } m/z$ 339 ($\text{M}+1$).

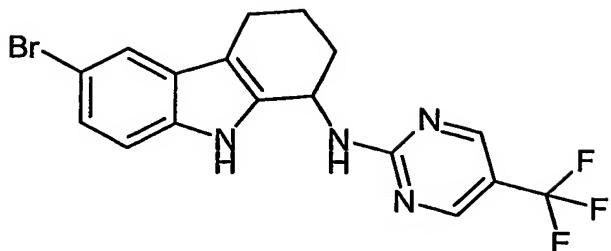
10

Example 32: 6-Bromo-*N*-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride



6-Bromo-*N*-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (50 mg, 0.19 mmol) and 4,6-dimethyl-2-chloropyrimidine (134 mg, 0.94 mmol) in a similar manner as described in Example 22 to give 12 mg (16%) of a yellow solid. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$): δ 10.98 (s, 1H), 8.40 (br s, 2H), 7.59 (s, 1H), 7.26 (d, 1H), 7.16 (d, 1H), 6.77 (s, 1H), 5.52-5.48 (m, 1H), 2.68-2.61 (m, 2H), 2.41 (2s, 6H), 2.15-2.06 (m, 1H), 2.04-1.96 (m, 1H), 1.91-1.76 (m, 2H); $\text{MS } m/z$ ($\text{M}+1$) 371, 373; ($\text{M}-1$) 369, 371.

Example 33: 6-Bromo-*N*-(5-(trifluoromethyl)pyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

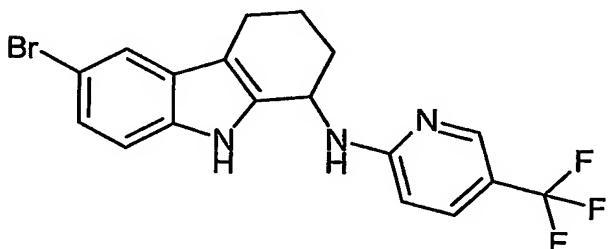


6-Bromo-N-[5-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (75 mg, 0.28 mmol) and 2-chloro-5-(trifluoromethyl)-pyrimidine (0.5 mL) in a similar manner as

5 described in Example 22 to give 5 mg (4%) of a yellow solid. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) taken at 80 °C: δ 10.94-10.88 (m, 1H), 8.69-8.62 (m, 1H), 8.30-8.24 (m, 1H), 7.55 (s, 1H), 7.21 (d, 1H), 7.13-7.10 (m, 1H), 7.02 (d, 1H), 5.40-5.27 (m, 1H), 2.62-2.58 (m, 2H), 2.08-1.96 (m, 2H), 1.87-1.76 (m, 2H); MS m/z (M-1) 409, 411.

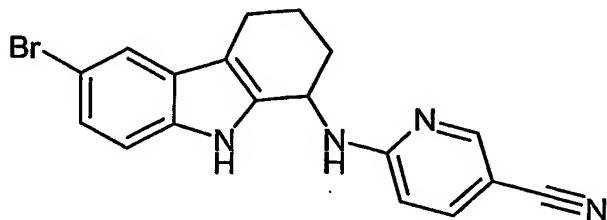
10 Example 34: 6-Bromo-N-[5-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine



6-Bromo-N-[5-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

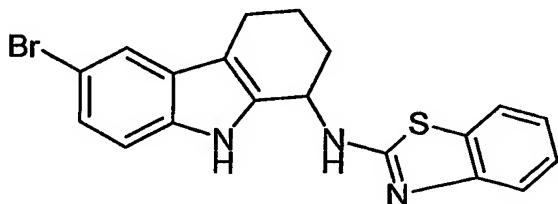
was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (75 mg, 0.28

15 mmol) and 5-(trifluoromethyl)-2-bromopyridine (192 mg, 0.85 mmol) in a similar manner as described in Example 22 to give 6.5 mg (6%) of a off-white solid. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$): δ 10.95 (s, 1H), 8.36 (s, 1H), 7.79 (d, 1H), 7.64 (dd, 1H), 7.57 (s, 1H), 7.23 (d, 1H), 7.13 (dd, 1H), 6.62 (d, 1H), 5.40-5.36 (m, 1H), 2.70-2.55 (m, 2H), 2.06-1.78 (m, 4H); MS m/z (M-1) 408, 410.

Example 35: 6-[(6-Bromo-2,3,4,9-tetrahydro-1H-carbazol-1-yl)amino]nicotinonitrile

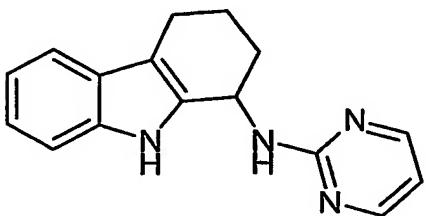
6-[(6-Bromo-2,3,4,9-tetrahydro-1H-carbazol-1-yl)amino]nicotinonitrile was prepared from 6-bromo-2,3,4,9-tetrahydro-1H-carbazol-1-amine (75 mg, 0.28 mmol) and 6-chloronicotinonitrile (118 mg, 0.85 mmol) in a similar manner as described in Example 22 to give 6.5 mg (6%) of a light brown solid. ¹H-NMR (DMSO-d₆): δ 10.95 (s, 1H), 8.36 (s, 1H), 7.79 (d, 1H), 7.64 (dd, 1H), 7.57 (d, 1H), 7.23 (d, 1H), 7.13 (dd, 1H), 6.62 (d, 1H), 5.40-5.35 (m, 1H), 2.70-2.55 (m, 2H), 2.07-1.78 (m, 4H); MS m/z (M-1) 365, 367.

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Example 36: N-(1,3-Benzothiazol-2-yl)-6-bromo-2,3,4,9-tetrahydro-1H-carbazol-1-amine

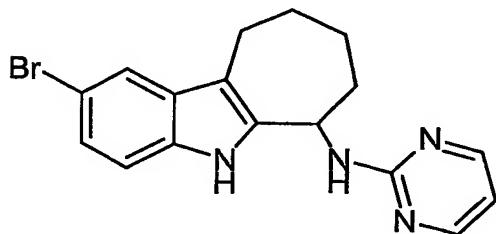
15

N-(1,3-Benzothiazol-2-yl)-6-bromo-2,3,4,9-tetrahydro-1H-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1H-carbazol-1-amine (75 mg, 0.28 mmol) and 2-chlorobenzothiazole (143 mg, 0.84 mmol) in a similar manner as described in Example 22 to give 11 mg (10%) of a yellow solid. ¹H-NMR (CDCl₃): δ 9.31 (s, 1H), 7.70-7.62 (m, 3H), 7.39 (t, 1H), 7.29-7.17 (m, 4H), 5.38-5.32 (m, 1H), 2.77-2.75 (m, 2H), 2.45-2.38 (m, 1H), 2.10-1.99 (m, 3H); MS m/z (M-1) 396, 398.

Example 37: N-Pyrimidin-2-yl-2,3,4,9-tetrahydro-1H-carbazol-1-amine

N-Pyrimidin-2-yl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (150 mg, 0.81 mmol) and 2-chloropyrimidine (184 mg, 1.62 mmol) in a similar manner as described in Example 22 to give 16 mg (8%) of a yellow solid. $^1\text{H-NMR}$ (DMSO- d_6): δ 10.63 (s, 1H), 8.32 (d, 2H), 7.43 (d, 1H), 7.36 (d, 1H), 7.25 (d, 1H), 7.01-6.97 (m, 1H), 6.93-6.89 (m, 1H), 6.60 (t, 1H), 5.32-5.28 (m, 1H), 2.68-2.57 (m, 2H), 2.04-1.97 (m, 2H), 1.87-1.75 (m, 2H).

10

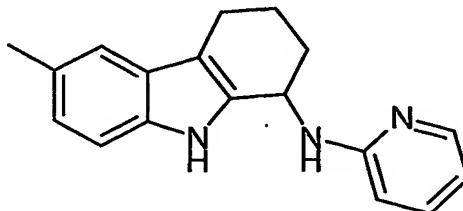
Example 38: 2-Bromo-N-pyrimidin-2-yl-5,6,7,8,9,10-hexahydrocyclohepta[b]indol-6-amine

2-Bromo-*N*-pyrimidin-2-yl-5,6,7,8,9,10-hexahydrocyclohepta[b]indol-6-amine was

15 prepared from 2-bromo-5,6,7,8,9,10-hexahydrocyclohepta[b]indol-6-amine (150 mg, 0.54 mmol) and 2-chloropyrimidine (123 mg, 1.07 mmol) in a similar manner as described in Example 22 to give 18 mg (9%) of a yellow solid. $^1\text{H-NMR}$ (DMSO- d_6): δ 10.80 (s, 1H), 8.31 (d, 2H), 7.57 (s, 1H), 7.49 (d, 1H), 7.20 (d, 1H), 7.07-7.04 (m, 1H), 6.60 (t, 1H), 5.36-5.33 (m, 1H), 2.94-2.89 (m, 1H), 2.70-2.63 (m, 1H), 2.05-1.94 (m, 2H), 1.89-1.59 (m, 4H); MS m/z (M+1) 357, 359; (M-1) 355, 357.

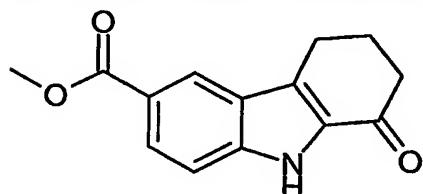
20

Example 39: 6-Methyl-N-pyridin-2-yl-2,3,4,9-tetrahydro-1H-carbazol-1-amine hydrochloride salt

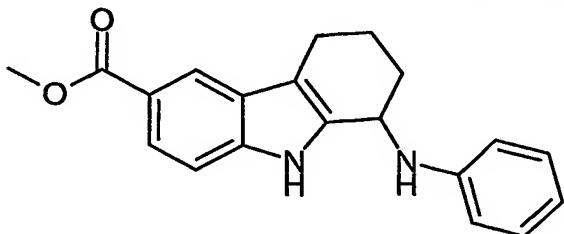


6-Methyl-N-pyridin-2-yl-2,3,4,9-tetrahydro-1H-carbazol-1-amine hydrochloride salt
 5 was prepared from 6-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (0.10 g, 0.5 mmol) and 2-aminopyridine (0.51 g, 0.55 mmol) in a similar manner as described above to give a brown solid (0.002 g, 1.0%). $^1\text{H-NMR}$ (CDCl_3): δ 8.72 (s, 1H), 8.23 (d, 1H), 7.48 (t, 1H), 7.32 (s, 1H), 7.20 (d, 1H), 7.00 (d, 1H) 6.69 (t, 1H), 6.49 (d, 1H), 5.25 (d, 1H), 4.71 (d, 1H) 2.80-2.75 (m, 2H), 2.40-2.28 (m, 1H), 2.09-1.91 (m, 3H); MS m/z 10 183 (M-94).

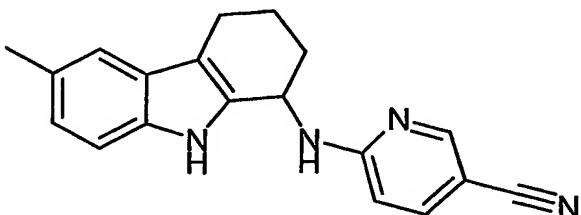
Example 40: Methyl 1-anilino-2,3,4,9-tetrahydro-1H-carbazole-6-carboxylate



Methyl 1-anilino-2,3,4,9-tetrahydro-1H-carbazole-6-carboxylate was prepared from 6-bromo-2,3,4,9-tetrahydro-1H-carbazol-1-one (0.05 g, 0.19 mmol), palladium acetate (0.04 g, 0.02 mmol), dppf (1,1'-Bis(diphenylphosphino)ferrocene) (0.01 g, 0.02 mmol) and triethylamine (0.025 mL, 0.19 mmol). The reagents were added to a round bottom flask with stir bar along with a 3:1 mixture of dimethyl sulfoxide:methanol (5.0 mL) and heated to 85 °C under atmospheric pressure of carbon monoxide for 4 hours. The solution was cooled to room temperature, water (5.0 mL) and ethyl acetate (25 mL) added, the layers separated and the organic layer washed with water (5.0 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated to yield an oil that was purified by chromatography (5-50% ethyl acetate/hexanes gradient) to yield a white solid (0.03 g, 65%). $^1\text{H-NMR}$ (CDCl_3): δ 9.35 (s, 1H), 8.46 (s, 1H), 8.05 (d, 1H), 7.45 (d, 1H), 3.95 (t, 3H), 3.06 (t, 2H), 2.69 (t, 2H) 2.30 (t, 2H); MS m/z 25 244 (M+1).

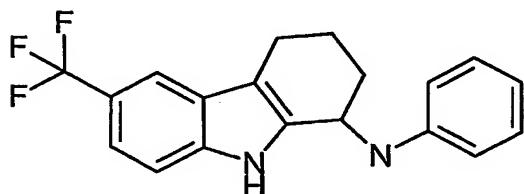
Example 41: Methyl 1-anilino-2,3,4,9-tetrahydro-1H-carbazole-6-carboxylate

Methyl 1-anilino-2,3,4,9-tetrahydro-1H-carbazole-6-carboxylate was prepared from 6-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (0.03 g, 0.11 mmol) and aniline (0.13 mL, 0.13 mmol) in a similar manner as described above. Further purification by reverse phase HPLC (Waters C18 Symmetry column, 50-90% acetonitrile/water over 8.5 min., 35 mL/min.) gave a yellow solid (0.005 g, 13%). ¹H-NMR (CDCl₃): δ 8.27 (s, 1H), 8.25 (s, 1H), 7.86 (d, 1H), 7.27 (t, 2H), 7.23 (d, 1H), 6.79 (t, 1H) 6.75 (d, 2H), 4.83 (t 1H), 3.93 (s, 3H) 2.78 (t, 2H), 2.28-2.20 (m, 1H), 2.07-2.00 (m, 1H), 1.92-1.80 (m, 1H); MS *m/z* 228 (M-93).

Example 42: 6-[(6-Methyl-2,3,4,9-tetrahydro-1H-carbazol-1-yl)amino]nicotinonitrile hydrochloride salt

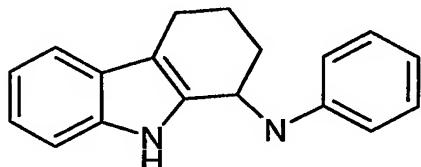
15 6-[(6-Methyl-2,3,4,9-tetrahydro-1H-carbazol-1-yl)amino]nicotinonitrile hydrochloride salt was prepared from 6-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-amine (0.10 g, 0.50 mmol) and 6-chloronicotinonitrile (0.138 g, 0.1 mmol) in a similar manner as described above to give a light brown solid (0.005 g, 3.0%). ¹H-NMR (CDCl₃): δ 8.49 (s, 1H), 8.33 (s, 1H), 7.56 (d, 1H), 7.28 (s, 1H), 7.18 (d, 1H), 6.99 (d, 1H), 6.42 (d, 1H), 5.31 (d, 1H), 5.15 (d, 1H) 2.77-2.70 (m, 2H), 2.28-2.25 (m, 1H), 2.00-1.92 (m, 3H); MS *m/z* 301 (M-1).

Example 43: *N*-Phenyl-6-(trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride

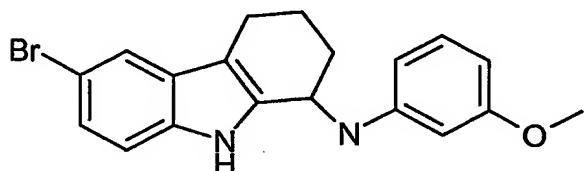


5 *N*-Phenyl-6-(trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine hydrochloride was prepared from 6-(trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (150 mg, 0.59 mmol) and aniline (110 mg, 1.2 mmol) in a similar manner as described above to give 15 mg (7%) of a white solid; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$): δ 11.36 (s, 1H), 7.77 (s, 1H), 7.46-7.30 (m, 4H), 7.14-7.10 (m, 2H), 6.81-6.58 (m, 2H), 4.83-4.80 (m, 1H), 10 2.75-2.58 (m, 2H), 2.08-1.80 (m, 4H); MS m/z (M-1) 329.

Example 44: *N*-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine



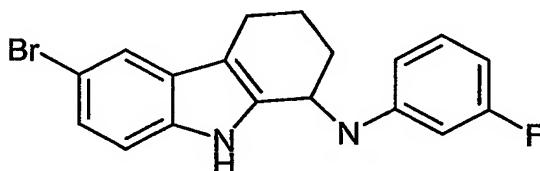
15 *N*-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 2,3,4,9-tetrahydro-1*H*-carbazol-1-one (150 mg, 0.81 mmol) and aniline (1.0 g, 11 mmol) in a similar manner as described above to give 24 mg (11%) of a white solid; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$): δ 10.83 (s, 1H), 7.40 (d, 1H), 7.28 (d, 1H), 7.09 (t, 2H), 7.03 (t, 1H), 6.94 (t, 1H), 6.72 (d, 2H), 6.54 (t, 1H), 5.91 (d, 1H), 4.79-4.75 (m, 1H), 2.73-2.67 (m, 1H), 20 2.64-2.57 (m, 1H), 2.01-1.73 (m, 4H); MS m/z (M-93) 170.

Example 45: 6-Bromo-N-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-N-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (100 mg, 0.38 mmol) and *m*-anisidine (94 mg, 0.76 mmol) in a similar manner as described above to give 37 mg (26%) of a white solid; ¹H-NMR (DMSO-*d*₆): δ 11.04 (s, 1H), 7.55 (s, 1H), 7.23 (d, 1H), 7.12 (dd, 1H), 6.97 (t, 1H), 6.32-6.27 (m, 2H), 6.13 (dd, 1H), 5.96 (d, 1H), 4.76-

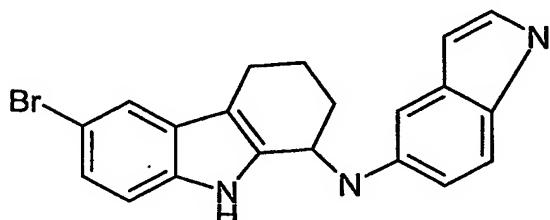
5 4.72 (m, 1H), 3.65 (s, 3H), 2.68-2.52 (m, 2H), 2.00-1.87 (m, 2H), 1.82-1.74 (m, 2H); MS *m/z* (M-1) 369, 371.

10

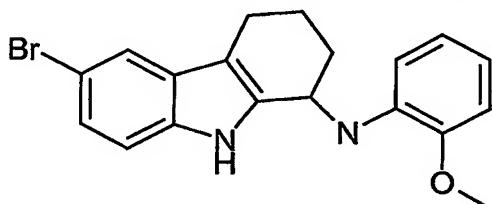
Example 46: 6-Bromo-N-(3-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-N-(3-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (100 mg, 0.38 mmol) and 3-

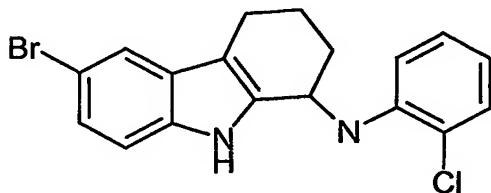
15 fluoroaniline (84 mg, 0.76 mmol) in a similar manner as described above to give 17 mg (12%) of a white solid; ¹H-NMR (DMSO-*d*₆): δ 11.08 (s, 1H), 7.56 (s, 1H), 7.23 (d, 1H), 7.14-7.04 (m, 2H), 6.53-6.48 (m, 2H), 6.36-6.26 (m, 2H), 4.78-4.76 (m, 1H), 2.69-2.53 (m, 2H), 2.00-1.85 (m, 2H), 1.81-1.76 (m, 2H); MS *m/z* (M+1) 357, 359.

Example 47: 6-Bromo-N-(1H-indol-5-yl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine

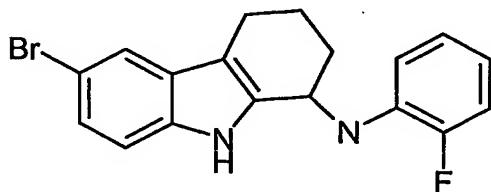
6-Bromo-N-(1H-indol-5-yl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine was prepared
 5 from 6-bromo-2,3,4,9-tetrahydro-1H-carbazol-1-one (100 mg, 0.76 mmol) and 5-
 aminoindole (100 mg, 0.76 mmol) in a similar manner as described above to give 54
 mg (37%) of a white solid; $^1\text{H-NMR}$ (DMSO- d_6): δ 11.08 (s, 1H), 10.61 (s, 1H), 7.55
 (d, 1H), 7.23 (d, 1H), 7.14-7.11 (m, 2H), 7.10 (d, 1H), 6.84-6.83 (m, 1H), 6.65 (dd,
 1H), 6.18-6.17 (m, 1H), 5.21 (d, 1H), 4.77-4.71 (m, 1H), 2.68-2.54 (m, 2H), 2.02-1.89
 10 (m, 2H), 1.84-1.73 (m, 2H); MS m/z (M+1) 378, 380.

Example 48: 6-Bromo-N-(2-methoxyphenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine

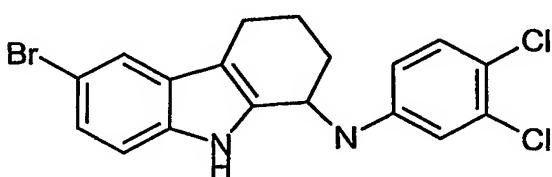
6-Bromo-N-(2-methoxyphenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine was prepared
 15 from 6-bromo-2,3,4,9-tetrahydro-1H-carbazol-1-one (200 mg, 0.76 mmol) and *o*-
 anisidine (187 mg, 1.52 mmol) in a similar manner as described above and
 recrystallized from acetonitrile to give 30 mg (11%) as yellow crystals; $^1\text{H-NMR}$
 (DMSO- d_6): δ 11.07 (s, 1H), 7.56 (d, 1H), 7.22 (d, 1H), 7.13 (dd, 1H), 6.84-6.73 (m,
 3H), 6.60-6.56 (m, 1H), 4.85-4.80 (m, 1H), 4.72 (d, 1H), 3.73 (s, 3H), 2.70-2.53 (m,
 20 2H), 2.00-1.75 (m, 4H); MS m/z (M-1) 369, 371.

Example 49: 6-Bromo-N-(2-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-N-(2-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (200 mg, 0.76 mmol) and 2-chloroaniline (193 mg, 1.51 mmol) in a similar manner as described above to give 43 mg (15%) of a white solid; ¹H-NMR (DMSO-*d*₆): δ 11.08 (s, 1H), 7.57 (d, 1H), 7.27-7.23 (m, 2H), 7.16-7.12 (m, 2H), 6.92 (d, 1H), 6.64-6.60 (m, 1H), 5.12 (d, 1H), 4.95-4.90 (m, 1H), 2.71-2.56 (m, 2H), 2.04-1.76 (m, 4H); MS *m/z* (M-1) 373, 375.

10 Example 50: 6-Bromo-N-(2-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

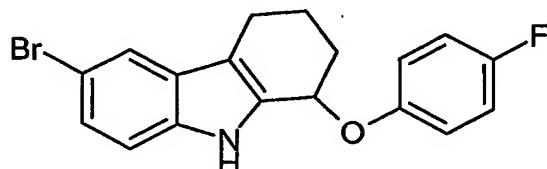
6-Bromo-N-(2-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (200 mg, 0.76 mmol) and 2-fluoroaniline (168 mg, 1.51 mmol) in a similar manner as described above to give 37 mg (14%) of a white solid; ¹H-NMR (DMSO-*d*₆): δ 11.04 (s, 1H), 7.55 (d, 1H), 7.23 (d, 1H), 7.12 (dd, 1H), 7.05-6.85 (m, 3H), 6.59-6.54 (m, 1H), 5.53 (m, 1H), 4.87-4.82 (m, 1H), 2.68-2.57 (m, 2H), 2.04-1.92 (m, 2H), 1.87-1.72 (m, 2H).

20 Example 51: 6-Bromo-N-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine

6-Bromo-N-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine was prepared from 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (200 mg, 0.76 mmol) and 3,4-dichloroaniline (245 mg, 1.51 mmol) in a similar manner as described above

to give 12 mg (4%) of an off-white solid; $^1\text{H-NMR}$ (DMSO- d_6): δ 11.08 (s, 1H), 7.57 (d, 1H), 7.26 (d, 1H), 7.23 (d, 1H), 7.13 (dd, 1H), 6.92 (d, 1H), 6.70 (dd, 1H), 6.52 (d, 1H), 4.79-4.77 (m, 1H), 2.68-2.52 (m, 2H), 1.99-1.72 (m, 4H); MS m/z (M-1) 409.

5 Example 52: 6-Bromo-N-(4-fluorophenoxy)-2,3,4,9-tetrahydro-1*H*-carbazole



a) 6-Bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol.

To a solution of 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (500 mg, 1.9 mmol) in methanol (20 mL) was added sodium borohydride (144 mg, 3.8 mmol) portionwise.

10 The reaction mixture was stirred for one hour and quenched with water (5 mL). The reaction was concentrated, diluted with methylene chloride and washed with water. The organic phase was concentrated and the crude alcohol purified by flash chromatography on silica (5% to 30% ethyl acetate/hexanes gradient) to provide 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol (255 mg, 50%) as a light brown solid: $^1\text{H-NMR}$ (DMSO- d_6): δ 10.99 (s, 1H), 7.54 (d, 1H), 7.25 (d, 1H), 7.12 (dd, 1H), 5.18 (d, 1H), 4.75-4.70 (m, 1H), 2.64-2.53 (m, 2H), 2.02-1.91 (m, 2H), 1.77-1.66 (m, 2H); MS m/z (M-1) 339, 341.

b) 6-Bromo-N-(4-fluorophenoxy)-2,3,4,9-tetrahydro-1*H*-carbazole.

20 To a solution of 6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol (50 mg, 0.19 mmol) in THF (5 mL) was added *p*-fluorophenol (43 mg, 0.38 mmol), polymer supported triphenylphosphine (1.67 mmol/g, 228 mg, 0.38 mmol) and diisopropyl azodicarboxylate (77 mg, 0.38 mmol). The reaction was stirred at room temperature for 16 h, and additional diisopropyl azodicarboxylate (77 mg, 0.38 mmol) was added.

25 The reaction was stirred for 16 h, filtered and concentrated. The crude product was purified by flash chromatography on silica (2% to 20% ethyl acetate/hexanes gradient) to provide 6-bromo-N-(4-fluorophenoxy)-2,3,4,9-tetrahydro-1*H*-carbazole (8 mg, 12%) as a white solid: $^1\text{H-NMR}$ (DMSO- d_6): δ 11.20 (s, 1H), 7.61 (d, 1H), 7.26 (d, 1H), 7.16-7.06 (m, 5H), 5.53 (t, 1H), 2.75-2.69 (m, 1H), 2.57-2.50 (m, 1H), 2.02-1.76 (m, 4H).

30

BIOLOGICAL EXPERIMENTALS AND DATA

Compounds of the current invention are believed useful in the treatment and/or prophylaxis of conditions and diseases associated with HPV infection. Activity mediated through HPV was determined using the following W-12 cellular assay.

Cell culture and medium

The W12 cell line used contains HPV16 DNA and was derived from a low-grade cervical dysplasia tissue by Margaret Stanley and subsequently clonally selected by Paul Lambert (University of Wisconsin). One of these clones, W12-20850, contains

10 1000 copies of episomal HPV16 DNA and was used in the cell-based assay. W12-20850 cells were routinely cultured with a gamma-irradiated (6000 rads) feeder layer of 3T3 cells. Assays, however, were run in the absence of a 3T3 feeder layer. W12-20850 and 3T3 cells were routinely split when they were sub-confluent. W12-20850 were grown in W12 Medium which is constituted of 25% DMEM (Gibco BRL, Cat # 12430-047), 75% F12 Media (Gibco BRL, Cat # 11765-021) and 2.5% FBS. The additives include 24.0 m g/ml Adenine (Sigma, Cat # A-9795), 0.4 m g/ml Hydrocortisone (Calbiochem, Cat # 386698), 5.0 mg/ml Bovine Insulin (Sigma, Cat # I-1882), 8.4 ng/ml cholera toxin (Fluka, Cat # 26694) and 10ng/ml EGF (Invitrogen, Cat # 13247-051). 3T3 cells were grown in DMEM containing 10% FBS. Cell lines 20 were incubated at 37°C, in the presence of 5% CO₂.

Cell based assay

For the assay, W12-20850 cells were seeded into a 96 well plate-containing compound. Plates were incubated at 37°C in the presence of 5% CO₂, for four days. On the fourth day, cells were lysed and the amount of episomal HPV-16 DNA was 25 quantified using a non-radioactive hybrid capture technique with HPV-16 specific capture and detection probes. The percent inhibition relative to untreated control cells was then determined.

Hybrid capture

The hybrid capture assay is run in a 96 well plate format. Hybridization plates (Nunc 30 Maxisorb Cat # 450320) were coated with a mixture of capture probe and ReactiBind solution for at least 4 hours and then washed with 0.2X SSC, 0.05% Tween20 (SSCT) prior to blocking with 150 µl /well of 0.2 N NaOH, 1% Igepal, 10 mg/ml hsDNA for 6-8 hours. The hybridization was carried out by mixing 27 µl of lysed cells with 45 µl of denatured detection probe in 6M guanidine isothiocyanate. To prevent evaporation, 50 µl of mineral oil was added to each well. The plate was then heated

to 90°C for 6.5 minutes and the hybridization continued at 42°C overnight. Assay plates were washed 6 times with SSC/T. Anti-digoxigenin HRP-conjugated Ab (Boehringer Mannheim 1207733, 1:5000) was incubated in the wells for 30 min at room temperature and washed with PBS/0.05% Tween-20. SuperSignal LBA substrate (Pierce Cat # 37070) was added, and chemiluminescence was measured using Wallac 1420 Victor plate reader.

Example	W-12 (nM)	Example	W-12 (nM)	Example	W-12 (nM)
13	10	26	62	39	
14	<10	27	37	41	
15	10	28	15	42	
16	14	29	252	43	51
17	23	30	NA	44	
18	19	31	70	45	<10
19	<10	32	12	46	<10
20	<10	33	44	47	112
21	<10	34	<10	48	57
22	97	35	30	49	<10
23	44	36	72	50	70
24	30	37	4500	51	22
25	35	38	<10	52	

Test compounds were employed in free or salt form.

10 All research complied with the principles of laboratory animal care (NIH publication No. 85-23, revised 1985) and GlaxoSmithKline policy on animal use. Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.